Cule-H06052-25-P25364

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Second class postage paid, Rahway, NJ. Postmaster: senc address changes to: *British Journal of Ophthalmology*, c/ Mercury Airfreight International Ltd Inc, 2323 Randolp Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd

British Journal of Ophthalmology, 1992, **76**, 193–194

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Sarcoidosis and inflammatory eye disease

Two papers in the recent issues of *BJO* raise different aspects of the relationship between sarcoidosis and inflammatory eye disease. Rothova *et al*,[1] in a prospective study of the frequency of positive diagnosis of systemic disease association with various forms of uveitis, show that sarcoidosis was the commonest disease association albeit a small one 7%. Karma *et al*[2] address the problem of the pathogenesis of sarcoidosis by studying the cellular infiltrate in conjunctival biopsies of patients with sarcoidosis. Their studies have shown that the infiltrate in the conjunctiva is predominantly of the T cell phenotype with considerably more CD4+ T helper cells compared with CD8+ T suppressor cells than in normal control tissue. These results agree with similar studies of sarcoidosis in other tissues and point to the predominant role for the CD4+ T cell in the pathogenesis of the disease. The cellular composition of the epithelioid granuloma in sarcoidosis however, also contains a large number of monocyte/macrophages in addition to CD4+ T cells.[3]

The association of sarcoidosis with inflammatory eye disease has been a difficult one for clinicians. On the one hand sarcoid involvement of the ocular tissue can be widespread from the lids and lacrimal apparatus to the optic nerve and the chiasm. On the other hand when a specific tissue is involved, such as in retinal vasculitis or optic neuritis, the condition mimics closely the disease as it occurs in the absence of sarcoidosis and the only evidence for the link is guilt by association. Since we know little about the nature of the immunological dysfunction in sarcoidosis there is almost a case for ignoring the association and treating the eye condition for what it represents.

Pathologically the granulomatous lesions which are produced in the ocular and non-ocular tissues are remarkably similar particularly with regard to the nature of the cellular infiltrate. CD4+ T cells are a significant component of the granulomata and occur usually as a rim of surrounding cells with epithelioid giant cells, macrophages, and other MHC Class II positive cells forming the core of these non-caseating lesions. In the lung it has been shown that antigen presentation by macrophages to T cells is significantly enhanced[4] and it is possible that the granulomatous lesions represent mini-'antigen-presentation factories' in which antigen-presenting cells such as dendritic cells and macrophages constantly present antigen to CD4+ T cells. The avid adherence of several T cells to single macrophages has been a repeated observation in bronchiolar lavage specimens from patients with sarcoidosis but the significance of this has not been elucidated.[5] Interestingly steroid treatment of sarcoid patients reduces the number of these macrophage-lymphocyte aggregates and converts the adherent lymphocytes from CD4+ activated T cells to CD8+ suppressor cells.[6]

CD4+ T cells are the primary cell mediators of immune responses and there is a high turnover of T cells as well as other cells in the microgranuloma. It is thus simple to visualise perpetuation of the disease by release of antigen-specific T cell from these cell 'factories' into the surrounding tissues. The similarity in the pathomorphology of sarcoid lesions to other granulomatous lesions such as the Dalen-Fuch's nodule of sympathetic ophthalmia[7] and many other ocular and non-ocular diseases is such that a general mechanism for the pathogenesis of these diseases can be envisaged, based on the local presentation of tissue and/or foreign antigen within these macrophage-lymphocyte clusters in the granulomata. In most cases the nature of the antigen is unknown; in theory at least, however, it should be possible to close in on the hunt for the antigen(s) by isolating and/or cloning antigen-specific cells from these lesions.

Thus we can see the value of studies such as those described in these two papers.[1,2] Apart from documenting the nature and types of cells present in the tissues, they point the way towards strategies for investigating elusive diseases such as sarcoidosis. If it is correct that up to 70% of patients with sarcoidosis have cellular infiltrates and/or granulomatous lesions[8] in the conjunctiva, irrespective of the presence of eye disease, it should be a simple matter to obtain material for study and cell culture.

Apart from the value of such studies in furthering our understanding of disease processes, they help to remind us of their use diagnostically. The diagnosis of sarcoidosis often rests on some rather indirect tests such as serum angiotensin converting enzyme or lysozyme.[9] In some instances it can be very difficult to attach a clear diagnosis of sarcoidosis to a particular case, such as one in which there is evidence of endogenous uveitis with some hilar lymphadenopathy and little else of diagnostic aid. In such circumstances even a quadriceps muscle biopsy has been performed, itself a simple procedure. A conjunctival biopsy is an even simpler test and, with frozen-section immunostaining, might help significantly in establishing the diagnosis. The corollary, however, is that a negative biopsy does not exclude the diagnosis.

J V FORRESTER

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Announcement

Professor John V Forrester takes over as Editor of the *British Journal of Ophthalmology* from the beginning of April 1992. Mr Redmond Smith is retiring. Papers submitted to the journal for publication should now be sent to Professor Forrester at the Department of Ophthalmology, Medical School, Foresterhill, Aberdeen AB9 2ZD, Scotland.

British Journal of Ophthalmology, 1992, **76**, 195–197

ORIGINAL ARTICLES

The treatment of periocular basal cell carcinomas by radiotherapy

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Accepted for publication
29 August 1991

Abstract

Experience in the treatment of periocular basal cell carcinoma is described. Excellent local control rates and minimal morbidity have been achieved in a series of 128 tumours occurring in 127 patients with a minimum 3 year follow-up.

The role of radiotherapy in the management of skin cancer is well established,[1] but the management of basal cell carcinoma of the eyelid is controversial. There is a reluctance among some ophthalmologists to refer patients for radiotherapy because of the fear of serious complications and a high failure rate. This is undoubtedly due to the calamities attendant on the use of radiotherapy in the early part of this century. An analysis of a series of 127 patients treated by a standard 5-day course of outpatient superficial radiotherapy reveals a 100% local control rate with a minimum 3-year follow-up. The minor complication rate was low and there were no serious complications. The cosmetic result was generally good and probably better than surgery could have achieved, particularly when lid reconstruction would have been required for larger lesions. A review of the literature indicates comparable results. Radiotherapy provides a safe simple outpatient alternative to surgery. Anaesthesia and highly skilled reconstructive surgery can be avoided in an often elderly group of patients.

Materials and methods

We report on a series of 127 patients referred to the Sussex Radiotherapy and Oncology Centre, Royal Sussex County Hospital, Brighton between 1974 and 1988. One hundred patients were previously untreated, eight had histologically incomplete excisions, and 19 had frank post-surgical recurrences. The diagnosis was not considered in doubt by the referring clinician or radiotherapist in the eight remaining cases.

Table 1 shows the regional distribution of the tumours and Table 2 the age distribution. Table 3 shows the size distribution of the lesions.

All our patients were treated with a standard fractionation regimen and each lesion was treated with a dose of 3400 cGy given in five consecutive daily fractions of 680 cGy using a 90 keV beam. A minimum margin of 0·5 cm around the visible lesion was employed and the underlying eye was protected with a lead internal eyeshield (Figs 1 and 2).

Table 1 Basal cell carcinoma. Distribution of 128 lesions in 127 patients

Site	*Number*	*Percentage*
Upper lid	1	<1
Lower lid	79	61·8
Medial canthus	36	28·1
Lateral canthus	12	9·3
Total	128	100·0

Table 2 Basal carcinomas of eyelids and canthi. Age incidence of cases

Average age	62·5
Youngest	40
Oldest	94

52 of 127 patients (40·6%) were older than 75 years

Table 3 Size of lesion by largest diameter

Size	<1 cm	1 cm	1·5 cm	2·0 cm	2·5 cm	>3·0 cm
Number of lesions	40	37	24	19	7	1

The majority of lesions were 2·0 cm or less in diameter and ideally suited to this particular treatment schedule. Lesions more than 3·0 cm would require more protracted treatment courses in order to achieve the best tumour control with acceptable morbidity. Table 4 shows how our

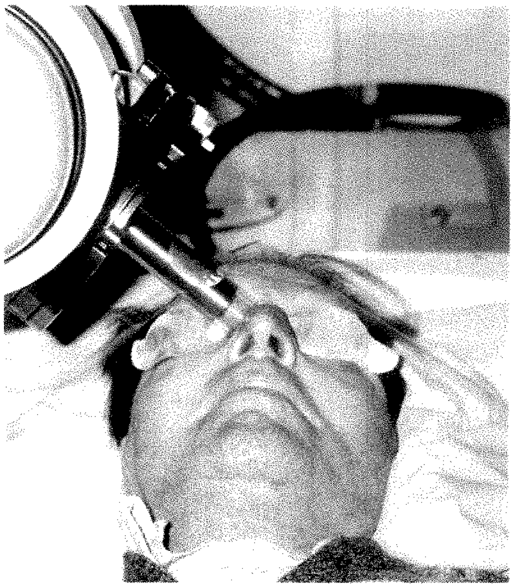

Figure 1 Showing treatment set-up and shielding of contralateral eye when irradiating a lesion at the medial canthus.

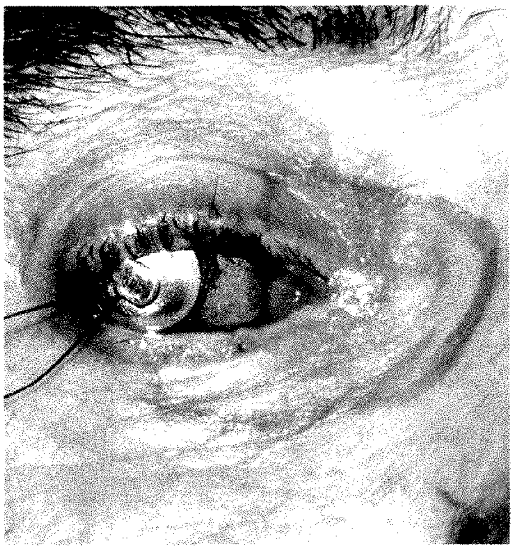

Figure 2 Acrylic coated lead internal eyeshield employed to protect the eye.

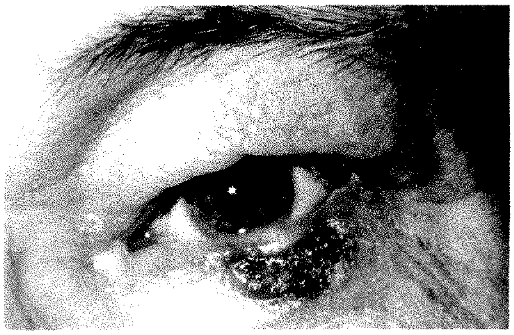

Fig 3A

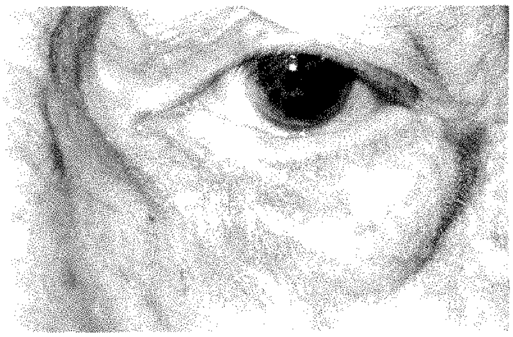

Fig 3B

Figure 3 Tumour before radiotherapy (A) and after treatment (B) showing excellent tumour response and good cosmetic result.

local control and recurrence-free rates compare with other radiotherapy series. Figure 3 illustrates a typical pre- and post-treatment result.

Complications

In 1948 Duke-Elder and Parsons stated that, for eyelid tumours, excision should be the rule and radiation the exception,[5] however, by 1974 these views had profoundly altered and they considered[6] that 'excision or radiotherapy are probably equally effective when efficiently carried out.' It is undoubtedly the fear of radiation complications that is the main reason for preferring surgery to radiation therapy. In our series complications of treatment have been minimal and are listed in Table 5.

Moderate skin changes and epilation are viewed as equivalent to a surgical scar and are not considered as complications. Ectropion is often present before treatment and epiphora is frequently seen at presentation with lesions of the medial canthus. Two of our patients developed canalicular stenoses following treatment of lesions involving the lower punctum and canaliculus which would have required excision of these structures had surgery been undertaken. Mustarde[7 8] has stated that in reconstructive surgery of the medial canthus it is possible to remove the lacrimal passages completely without epiphora, which is only likely to occur in the presence of conditions causing excessive tear formation such as a high wind, excessive exposure of the conjunctiva, and inflammatory conditions involving the lid margin, conjunctiva, cornea or lacrimal sac. Keratinisation of the tarsal conjunctiva occurred in 7% of cases. It is potentially a much greater problem when the centre of the upper lid is affected as the keratin plaque may abrade the cornea and patients may require a haptic contact lens to protect the cornea.

Despite the above list of potential complications the results from radiotherapy are excellent both in terms of tumour control and cosmetic result as shown in Table 6.

Prevention of complications

Patients who have an eyelid tumour irradiated invariably develop a radiation reaction in the treated area. While this reaction ultimately subsides the related bulbar conjunctiva and the cornea may be affected despite the presence of a lead contact lens during treatment. Antibiotic

Table 4 Local control

Series	No irradiated	Treatment failures	No of recurrences controlled by re-irradiation	NED 4 years or longer
Brighton	128	0		93/93 (100%)
Hahnemann[2]	444	20	2	426/444 (95·9%)
RMH[3]	630	39		590/630 (94·3%)
PMH[4]	1062	53		1009/1062 (95%)

RMH = Royal Marsden Hospital.
PMH = Princess Margaret Hospital, Toronto.

Table 5 Complications of treatment

Complication	PMH	RMH	Brighton
Lid necrosis	–	2·9%	–
Epiphora	27%	–	2·5%
Keratinisation	21%	5·6%	7%
Cataract	11%	0·8%	–
Corneal ulceration	–	1·6%	–
Ectropion	36%	–	<5%
Skin atrophy	64%	–	16%

Table 6 Cosmetic result

	PMH		Brighton	
	1 year	5 years	1 year	5 years
Excellent	323	107	115	86
Good	23	23	4	2
Fair	19	7	3	1
Poor	23	1	–	–
Not known	117	367	6	39

Table 7 Surgical series

	No treated	*Frozen section*	*Recurrence rate*	*Local control*
Doxanas[11]	165	39	0	100%
			7/126	94·5%
Payne *et al*[12]	273	0	42/199	79% at 6/12
Collin[9]	261	0	3/176 after primary surgery	95·8% 6 dead
Chalfin[13]	53	53	0	100%
Frank[10]	165	165	3	97·8%

eyedrops are routinely employed to avoid any infection, particularly in those cases where an internal eyeshield has been employed.

Discussion

The results of treatment in our series reveal no recurrences thus far in a group of patients who have been treated in identical fashion with meticulous attention to the treatment set-up. For small lesions of T1 category, of which there were 101 in our series, we would argue that radiotherapy is the treatment of choice. However it is also this group[7,8] who are suitable for an operation not requiring major plastic reconstruction. However our remaining patients, many of whom were elderly, would have required plastic reconstructive procedures with all that that entails in terms of availability of the requisite surgical skills and the surgical risks to the elderly frail patient.

Table 7 records some of the major surgical series. In three of these frozen section control of the margins was undertaken adding considerably to the duration of the procedure. In Collin's series[9] 71·2% of patients had either a flap or a graft procedure, yet 96% of the lesions were T1 by stage and eminently suitable for local radiotherapy; Frank,[10] in her series employing frozen section control, used flaps or grafts in more than 50% of cases. The results of both radiotherapeutic and surgical treatment are similar but, in view of the complexity of the surgical procedures that have to be employed even for small radiocurable tumours, we would submit that radiotherapy when performed with meticulous attention to the tumour margins and with every care taken to minimise morbidity is the treatment of choice for the majority of basal cell carcinomas of the eyelid, though surgery has an important role in the management of upper eyelid lesions and extensive tumours at the medial canthus whose deep margins may be assessable only at surgery. These tumours if they recur may spread deeply into the orbit and sinuses necessitating exenteration for cure.[14] The patients' interests are best safeguarded by ensuring close collaboration between ophthalmologists, plastic surgeons, radiotherapists, and dermatologists so that therapeutic approaches based on a partisan approach are avoided if possible. Each tumour must be judged on its merits and the most appropriate modality for each patient carefully decided.

Recurrence after previous radiotherapy should be treated surgically as the risk of radiation necrosis is excessive. However Lafontan *et al*[15,16] using interstitial radiotherapy techniques have successfully treated radiation failures, but this technique is not readily available and requires considerable expertise.

The rare lesion in the middle third of the upper eyelid constitutes a relative contraindication to radiation due to the probable risk of tarsal keratinisation and the risk of corneal damage and we do not routinely irradiate these lesions. However if a lesion on the upper lid is sufficiently large to require an extensive plastic procedure then radiotherapy becomes an attractive alternative, as keratinisation does not invariably ensue and a contact lens may suffice to protect the cornea adequately. If the eyelid tumour is related to a damaged or abnormal cornea the risk of further damage to the cornea from irradiation changes in the eyelid should lead one to consider surgery as the favoured treatment. The advanced basal cell carcinoma with bone involvement is rarely eradicated by radiotherapy and is best treated by a course of radical radiotherapy followed by radical surgery.

Conclusion

Our data show meticulously planned superficial radiotherapy to be a highly effective treatment for periocular basal cell carcinoma with excellent control rates and minimal morbidity in often elderly patients. We do not dismiss surgery but regard surgery and radiotherapy as complementary modalities.

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British Journal of Ophthalmology, 1992, 76, 198–201

Impression cytology of conjunctival melanosis and melanoma

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Accepted for publication 22 August 1991

Abstract

Impression cytology using cellulose acetate paper has been used in various ocular surface disorders as a simple non-invasive diagnostic test. To assess its value in differentiating melanocytic tumours, 24 patients with a range of pigmented lesions of the conjunctiva were examined using this technique. Cytological and histological diagnoses were compared in 23 cases. In 73% of cases impression cytology predicted the histological diagnosis by detection of superficial atypical melanocytes and their proportion relative to benign epithelial cells. This pilot study shows impression cytology to be a useful diagnostic aid in the differentiation of pigmented tumours of the bulbar conjunctiva.

The management of pigmented lesions of the conjunctiva depends on the ability to distinguish between benign, premalignant, and frankly malignant conditions. Conjunctival malignant melanoma is uncommon but potentially lethal. Most conjunctival melanomas arise in association with pre-existing primary acquired melanosis (PAM).[1,2] It is important to recognise and monitor this precursor because of its malignant potential. Follow-up of suspicious conjunctival lesions by repeated biopsies may cause symblepharon, lid deformities, and discomfort to the patient.

Exfoliative cytology has been advocated as a diagnostic and monitoring tool without significant side effects.[3-6] Atypical melanocytes which have migrated to the epithelial surface can be detected by this technique which is fast, inexpensive, and less distressing to the patient than biopsy. However smears are open to misinterpretation.[6] Impression cytology with the aid of a piece of cellulose acetate filter paper was first utilised as a method for 'simple conjunctival biopsy'.[7] Since then the technique has been employed in the study of dry eyes,[8] squamous metaplasia,[9] and other surface disorders.[8]

Table 1 Patient details and diagnosis

Patient	*Age (years)*	*Laterality*	*Years of history*	*Impression (I)/ exfoliative (E) cytology (frequency)*	*Histological diagnosis*
1	27	L	20	2×I; 1×E	Naevus
2	32	L	1	2×I; 2×E	PAM+
3	54	R	3	2×I; 2×E	MM (PAM+)
4	75	L	6	2×I; 1×E	MM (PAM+)
5	51	R	10	2×I; 2×E	MM (PAM+)
6	64	R	2	2×I	MM (PAM+)
7	54	R	12	2×I	PAM+
8	58	L	16	2×I	MM (PAM+)
9	53	R	0·5	1×I	MM
10	57	R	1	2×I	PAM−
11	82	L	1	1×I	PAM+
12	31	L	18	1×I	Naevus
13	28	R	3	2×I	PAM−
14	40	L	20	1×I	Naevus
15	62	L	30	1×I	PAM+
16	89	R	?	1×I	PAM−
17	81	R	3	1×I	SAM
18	68	L	4	2×I	MM
19	33	R	7	2×I	PAM+, PAM−
20	58	R	0·5	1×I	SAM
21	61	R	2	1×I	MM (PAM+)
22	57	R	0·5	2×I; 2×E	PAM+
23	59	L	0·5	1×I	PAM+
24	42	R	2	1×I	MM

MM=malignant melanoma.
PAM+=primary acquired melanosis with atypia.
PAM−=primary acquired melanosis without atypia.
SAM=secondary acquired melanosis.
(PAM+)=originating from PAM+.

The aim of this study is to assess the value of impression cytology in differentiating benign, premalignant, and malignant conjunctival tumours.

Materials and methods

Impression cytology was carried out on pigmented conjunctival lesions of 24 consecutive patients attending the Oncology Clinic at Moorfields Eye Hospital in 1990 (Table 1). In addition exfoliative cytology was performed in six of these patients prior to conjunctival biopsy under general anaesthesia. Histological specimens were obtained from all patients either after the cytological examination or at least 3 months before. None of the patients had had adjuvant therapy such as cryotherapy before cytological examination or biopsy.

Impression cytology involves pressing a 2×6 mm cellulose acetate filter paper (Millipore) held by forceps onto the conjunctival surface with the aid of a small solid rod for 3 to 5 seconds (Fig 1). This painless procedure does not require topical anaesthesia. Tissue paper was used to absorb the inferior tear lake before sampling. After sampling the filter paper was placed in fixative solution containing glacial acetic acid, 37% formaldehyde, absolute ethyl alcohol, and distilled water. The specimens were stained with PAS/Papanicolaou, mounted on glass slides and embedded in DePeX (BDH).

For exfoliative cytology, cells were harvested by scraping the anaesthetised eye with the blunt side of a scapel blade. Subsequently they were smeared on to a glass slide and fixed with a cytological fixative aerosol spray (Comber and Son). The smears were stained with Giemsa (10% in buffer). Haematoxylin and eosin (H and E) and S-100 stained sections were prepared by the Department of Pathology, Institute of Ophthalmology for histological assessment of the specimens.

All cytological specimens were examined by two independent observers. An increased nuclear to cytoplasmic ratio (in comparison with keratinocytes), an irregular nuclear chromatin pattern, the presence of large nucleoli, and the finding of mitoses, anisokaryosis, and melanin were regarded as cytological features of malignancy. When the relative proportion of atypical melanocytes was low the lesion was cytologically diagnosed as pre-malignant melanosis equivalent to the histological diagnosis PAM with atypia as defined by Folberg *et al.*[2] If cancerous cells were abundant the diagnosis was malignant melanosis equivalent to malignant melanoma.

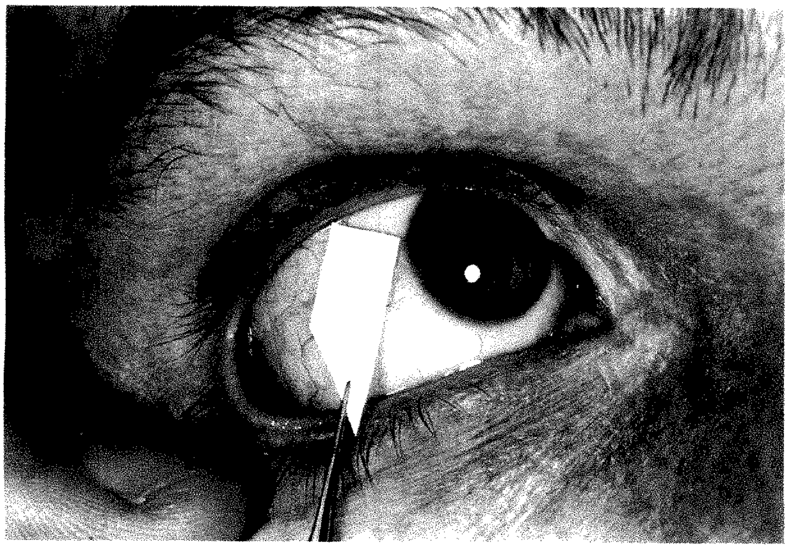

Figure 1 A cellulose acetate filter paper (Millipore) is applied to the bulbar conjunctiva of the right eye.

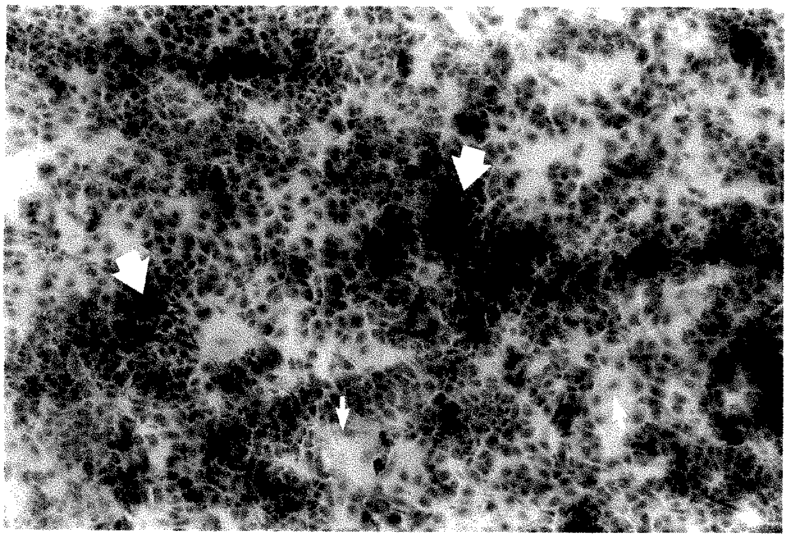

Figure 2 Abundant melanocytes (large arrows) with an increased nuclear to cytoplasmic ratio and intracellular melanin pigment granules are seen between keratinocytes (small arrows). Note the loss of goblet cells (see case report). (×50.)

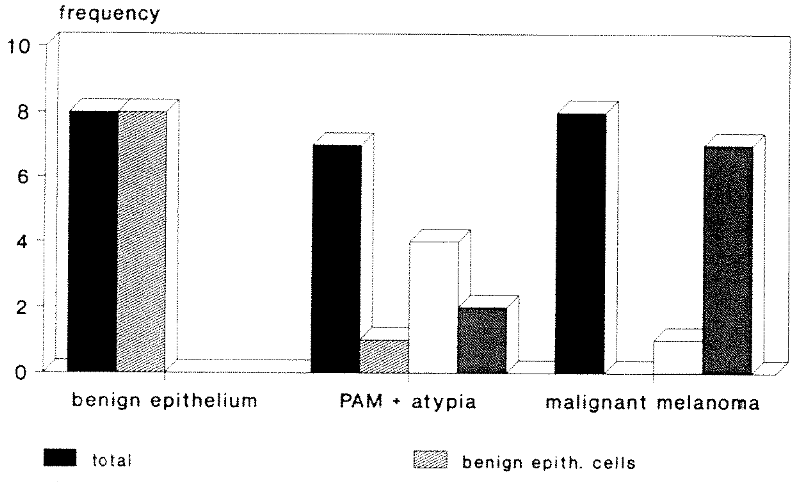

Figure 3 This histogram summarises the results of a comparison between the histological diagnosis (black bars, see horizontal axis) of 23 cases of conjunctival melanocytic lesions and the impression cytological diagnosis (striped/dotted bars, see legends).

Results

In 23 out of 24 cases (Table 1) an adequate number of cells including keratinocytes, goblet cells, and inflammatory cells was harvested by impression cytology (Fig 2). In one case of melanoma in the lower fornix (case 24) access to the lesion was difficult and the adherent cells were too sparse to make a conclusive diagnosis. Fig 3 shows that impression cytology detected atypical melanocytes in seven out of eight cases of malignant melanoma diagnosed with biopsy. In one case atypical melanocytes were present only in small groups and this lesion was diagnosed as premalignant melanosis. Four out of seven cases of PAM with atypia were correctly diagnosed; in one case only benign epithelial cells were found and two other cases were classified as malignant melanosis. Thus in 11 of 15 cases (73%) the histological diagnosis was predicted by impression cytology. Atypical melanocytes were not diagnosed in any of the cases of PAM without atypia and benign naevi.

Sufficient material was harvested by exfoliative cytology to make a cytological diagnosis in all six cases. Three out of four cases of PAM with atypia and malignant melanoma were predicted by this technique. In one case of PAM with atypia only keratinocytes and extracellular melanin were seen but no melanocytes. Neither of two benign lesions was mistaken for premalignancy or malignancy. The cytological features of individual cells were easier to recognise than in impression cytological specimens.

Case report

The use of impression cytology and exfoliative cytology of conjunctival malignant melanoma arising in an area of primary acquired melanosis is demonstrated by the following case.

A 73-year-old Caucasian woman was seen in the Oncology Clinic at Moorfields Eye Hospital in June 1988. She gave a 4 year history of gradually increasing pigmentation of the medial aspect of her right conjunctiva, caruncle, and skin of the medial canthus. On examination several flat pigmented areas were seen adjacent to a fleshy raised lesion supporting origin from PAM.

Biopsy of the caruncular element showed an inflamed cystic naevus and no evidence of frank malignancy. As a result of the biopsy she complained of double vision for 1 year. There were no further significant changes until July 1990 when multiple foci of nodular black tumour were noted in her fornices (Fig 4).

An impression cytological specimen of a nodule showed abundant atypical melanocytes (Figs 2 and 5), a finding which was confirmed by exfoliative cytology (Fig 6). The histological diagnosis in multiple incisional biopsies was predominantly epithelioid cell malignant melanoma and PAM with atypia (Fig 7).

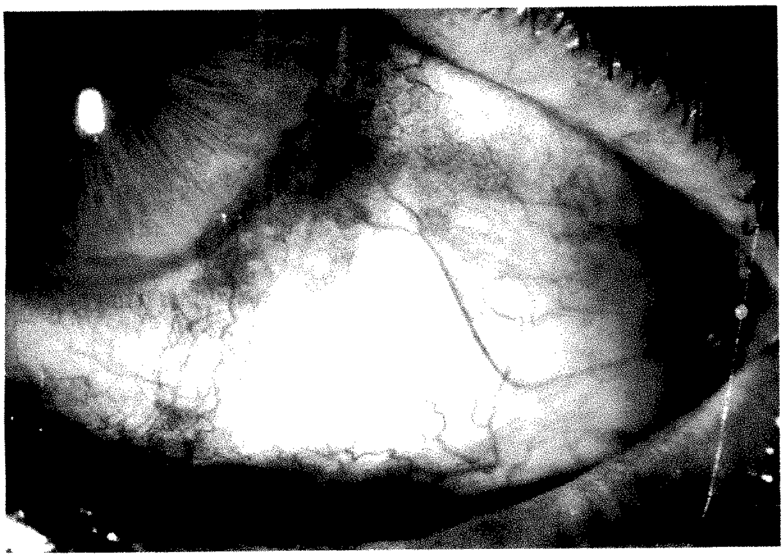

Figure 4 Flat epibulbar and caruncular melanosis and multiple foci of elevated melanocytic tumour in the lower fornix of the right eye (see case report).

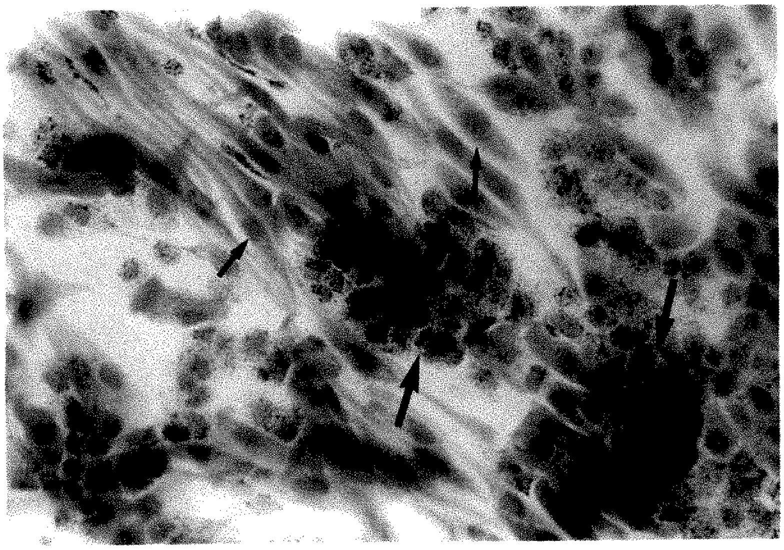

Figure 5 Impression cytological specimen (see case report) showing groups of small melanocytes (large arrows) with increased nuclear to cytoplasmic ratio, anisokaryosis, prominent eosinophilic nucleoli, and intracytoplasmic melanin pigment granules among elongated keratinocytes (small arrows). (×300.)

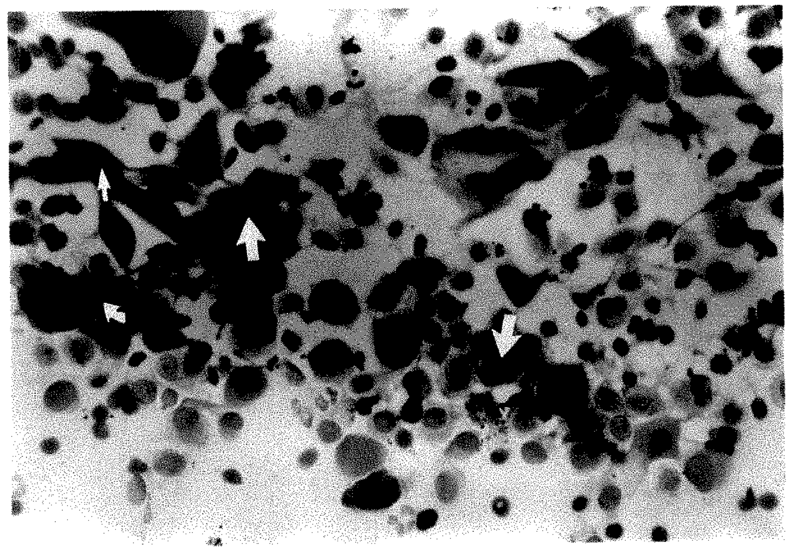

Figure 6 Scrape cytological specimen (see case report) showing keratinocytes (small arrow), inflammatory cells (curved arrow), and abundant atypical cells (large arrows) with anisokaryosis, enlarged nucleoli, intracytoplasmic melanin pigment granules, and irregular nuclear chromatin pattern. Occasionally mitotic figures are found. (×300.)

Systemic tests disclosed no evidence of metastatic disease and the right orbit was exenterated in October 1990. The exenteration specimen showed tumour cells within the lacrimal common canaliculus and at the medial canthal cutaneous resection margin. Subsequently the right orbit was irradiated. In February 1991 she developed spinal metastases which was treated with palliative radiotherapy, and she died of widespread metastases some weeks later.

Comment. The initial histological diagnosis of a raised nodule in an area of flat melanosis suggested the lesion was benign. As a result the lesion was not histologically re-assessed until it had extended to the fornices. Regular non-invasive monitoring of suspicious areas by cytology might have benefited this patient, who died three years after the first biopsy and within 6 months of orbital exenteration.

Discussion

The ascent of atypical melanocytes to the surface of the conjunctival epithelium is indicative of malignancy. Folberg *et al*[2] showed that PAM without atypia does not progress to frank melanoma whereas lesions with atypia tend to be incompletely excised and have a high recurrence rate.

Benign conditions such as conjunctival naevus and PAM without atypia are not associated with the ascent through conjunctival epithelium of atypical melanocytes, although benign cells from naevi growing actively in adolescence may be present in superficial conjunctival layers.[3] The lack of superficial melanocytes in benign naevi, PAM without atypia, and early stages of PAM with atypia means that they can only be diagnosed by histology with cytology only providing a 'negative' diagnosis in the absence of such cells.

Impression cytology is a quick, painless, non-invasive, inexpensive outpatient technique. The histological diagnosis was predicted correctly in 73% of 15 cases of malignancy or premalignancy. Previous work[6] has shown a similar percentage for exfoliative cytology. Repeated examinations may increase the sensitivity of this technique. A disadvantage in comparison with exfoliative cytology is the difficulty of focusing during microscopical examination and assessing cytological features due to the thickness of the filter paper. However the topographical distribution and relative proportion of atypical melanocytes could be better studied in impression cytology. A limitation of its use is the location of the pigmented lesion as access is a problem for tumours in the fornix and tarsal conjunctiva. In such cases examination by exfoliative cytology with a cotton wool swab and topical anaesthetic drops may be more appropriate.[5 6]

The results of the present study indicate that impression cytology could be used as a clinical monitoring tool in the follow-up of bulbar conjunctival tumours. Although a diagnostic biopsy remains necessary for determination of the origin and extent of those lesions, recurrent tumours, or suspicious areas might be biopsied less frequently thus reducing the risk of side effects and patients' discomfort. Impression cytology may also have a place in the investigation of other neoplastic lesions of the conjunctiva such as carcinoma in situ and squamous cell carcinoma.

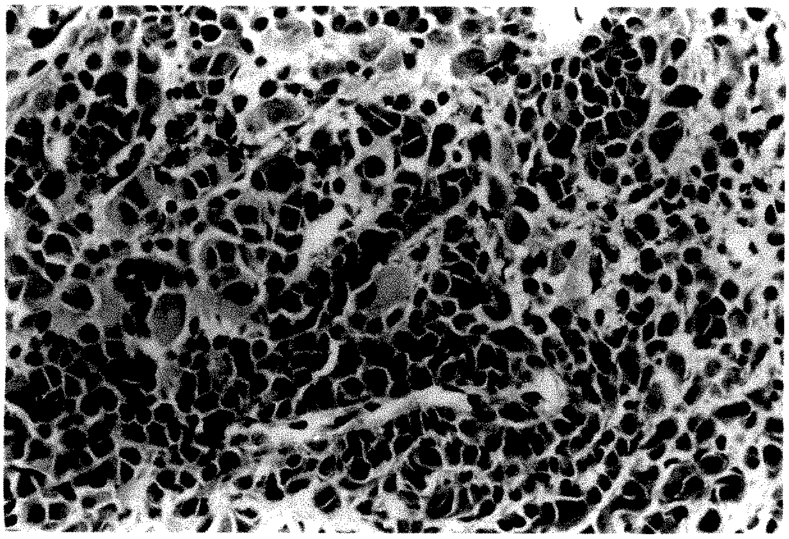

Figure 7 Histology (see case report) showing predominantly epithelioid cell malignant melanoma. (×150.)

Preliminary results of this study were presented at the 162nd Meeting of the Pathological Society of Great Britain and Ireland.

Dr A D A Paridaens was supported by grants from Foundations 'Stichting Fonds ter Bevordering van de Gezondheidszorg', 'Stichting De Drie Lichten' and 'Stichting Rens-Holle', The Netherlands.

We would like to thank Mr S Bailey, FRCS for his advice and for kindly providing the filter paper and fixative, and Mr C Elgueta for his help with the staining procedure.

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British Journal of Ophthalmology, 1992, **76**, 202–204

Retinopathy of prematurity in surfactant treated infants

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Accepted for publication
22 August 1991

Abstract

Seventy six babies of less than 1500 g birth weight who had surfactant replacement therapy for severe respiratory distress syndrome were studied to assess the presence and stage of subsequent retinopathy of prematurity (ROP). A control group of 90 babies, matched for birth weight and gestational age, who did not have surfactant therapy were also studied. Threshold ROP or greater was found in 1·7% of the surfactant group and 7·8% of the controls. For the babies of less than 1000 g birth weight 4·0% of the surfactant babies and 16·3% of the controls reached threshold disease or greater. It is concluded that surfactant therapy is not associated with an increased incidence or severity of severe ROP in this preterm population.

Retinopathy of prematurity (ROP) continues to be a potential major handicap for infants surviving neonatal intensive care. Its incidence and severity are greater in preterm infants of less than 1500 g birth weight or of less than 31 weeks' gestation. Neonatal respiratory distress syndrome (RDS) is due to surfactant deficiency and occurs predominantly in preterm infants of less than 32 weeks' gestation. Pulmonary surfactant is a complex mixture of phospholipids and proteins produced by type II alveolar pneumocytes; deficiency leads to alveolar collapse, ventilation-perfusion abnormalities, and hypoxaemia so that supplemental oxygen must be given to maintain arterial oxygen tension (PaO_2). Recent studies have shown that administration of exogenous natural surfactant to infants with RDS decreases neonatal mortality by 40%.[1] The administration of exogenous natural surfactant is associated with an acute rise in PaO_2. This can be closely monitored by pulse oximetry and the inspired oxygen concentration reduced rapidly to maintain an adequate PaO_2 and prevent hyperoxaemia. Following surfactant therapy there is improved gas exchange for at least the first 72 hours of life and subsequently a reduction in neonatal deaths.[1,2]

We were concerned that because of the increased survival rate of these extremely low birthweight babies associated with the large surge of PaO_2 at the time of surfactant delivery that there may be an increased risk of ROP.

Surfactant therapy has only recently been established as routine management in RDS and few data exist about the subsequent eye complications. We decided to study the incidence and severity of ROP in babies treated with surfactant for severe RDS and compare their outcome with that of less ill preterm babies who were not given surfactant. We have gathered ophthalmic data retrospectively from the records of those infants who received surfactant therapy at this institution from 1985–1990.

Materials and methods

Since 1985 data on all infants who have received surfactant therapy for severe RDS in our unit have been recorded on a computer database. The first 19 babies were enrolled in the Collaborative European Multicentre study of surfactant replacement therapy for severe RDS.[1] This extensive database has included all infants receiving surfactant therapy since the conclusion of this trial.

We used Curosurf a natural surfactant derived from porcine lung which was given in a dose of 200 mg/kg of phospholipid. All babies had intermittent positive pressure ventilation (IPPV) and were receiving more than 40–60% O_2.[1]

Because of the proved beneficial effects of surfactant therapy we were unable to use matched controls with severe RDS so we have used age and birthweight matched comparisons who did not receive surfactant therapy from the same time period.

All infants studied were managed in the neonatal intensive care unit of the Royal Maternity Hospital, Belfast which is a regional intensive care unit. All infants were examined by a paediatric ophthalmologist using indirect ophthalmoscopy following pupillary dilatation with phenylephrine 2·5% and cyclopentolate 1% eye drops. Their findings were documented in accordance with the International Classification of ROP,[3] that is, stage 1: a demarcation line; stage 2: ridge formation; stage 3: a ridge with extraretinal fibrovascular proliferation; stage 4: partial retinal detachment; stage 5: total retinal detachment. Threshold disease was defined as at least 5 contiguous clock hours or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of 'plus' disease (dilatation and tortuosity of the posterior retinal vessels). The infants were first examined at the equivalent of 32 weeks post-conceptional age and thereafter 2-weekly until 36 weeks and regression of any ROP was noted. If ROP was found then examination was weekly unless stage 2 'plus' or stage 3 was reached in which case examination was more frequently. Details of these examinations were retrieved retrospectively from the infants' records and added to the database.

Results

Seventy six babies of less than 1500 g birth weight and less than 31 weeks' gestational age were treated with surfactant. Fifty nine of these survived to 32 weeks' post-conceptional age allowing at least one eye examination. The control group consisted of 90 gestational age and birthweight matched babies who survived during the period of our study. These babies did not have severe RDS and did not receive surfactant. The characteristics of the groups are shown in Table 1.

Acute ROP developed in 15 (25·4%) of the surfactant group and 16 (17·8%) of the comparisons. The distributions of ROP for birth weight and gestational age are shown in Tables 2 and 3. Threshold disease or greater was reached one (1·7%) of the surfactant group and 7 (7·8%) of the comparisons; this difference was not significant.

Twenty five of the surfactant group were less than 1000 g birth weight with mean (SD) 834 (127) g and gestational age 26·3 (1·2) weeks. This compared with 43 in the control group with a mean birth weight of 823 (166) g and gestational age 27·1 (2·0) weeks. In these groups one (4·0%) of the surfactant group and seven (16·3%) of the controls developed threshold or greater ROP; again this difference was not significant.

In the full surfactant group six babies including the single baby with stage 4 disease died of late complications after 32 weeks post-conceptional age. Likewise three of the comparison group died late with stages 2, 3, and 4 disease respectively.

Table 1 Characteristics of surfactant treated and comparison babies surviving to examination

	Surfactant treated (n=59)	*Control (n=90)*
Birth weight (g)		
Mean (SD)	1046 (232)	1053 (269)
Gestational age (weeks)		
Mean (SD)	27·5 (1·7)	27·8 (1·9)
Male		
No (%)	38 (64)	39 (43)
Max FiO_2*		
Mean (SD)	0·76 (0·15)	0·56 (0·25)
IPPV†		
No (%)	59 (100)	62 (69)
Duration of O_2 (h)	1008	360
Median (range)	(172–5424)	(0–5208)
Mortality		
No (%)	6 (10)	3 (3)

*Fraction of inspired oxygen.
†Intermittent positive pressure ventilation.

Table 2 Distribution of ROP by birth weight in (A) surfactant treated babies and (B) comparisons

		*Stage**				
Birth weight (g)	*Total*	*No ROP*	*S1+2*	*S3*	*S3 'T'†*	*S4+5*
A						
<750	7	3	3	1	0	0
751–1000	19	14	3	1	0	1
1001–1500	33	27	6	0	0	0
B						
<750	13	5	3	1	2	2
751–1000	30	23	3	1	0	3
1001–1500	47	46	1	0	0	0

*International classification of ROP.
†Threshold.

Table 3 Distribution of ROP by gestational age in (A) surfactant treated babies and (B) comparisons

		*Stage**				
Gestational age (weeks)	*Total*	*No ROP*	*S1+2*	*S3*	*S3 'T'†*	*S4+5*
A						
23–27	31	19	9	2	0	1
28–31	28	25	3	0	0	0
B						
23–27	53	37	7	2	2	5
28–31	37	37	0	0	0	0

*International classification of ROP.
†Threshold.

Discussion

RDS is a common problem in the preterm neonate. Sixty five per cent of those babies of less than 1500 g develop RDS increasing to 80% of those less than 1000 g birth weight.[4] In this group hypoxia, hypercarbia, respiratory, and metabolic acidosis are commonplace. All these factors have been shown to be significantly associated with the development of acute ROP.[5 6 7] Many individual risk factors have been implicated in the genesis of ROP suggesting that the common thread is neonatal illness with disturbed homeostasis upsetting the delicately balanced process of retinal development.[7] Progression of ROP to advanced disease also seems to be largely determined by the severity of the early insult to the immature retina and is less influenced by prolonged or subsequent adverse effects.[6] Surfactant therapy in the first 48 hours of life has been shown to have been a significant advance in improving the survival rate of these particularly sick neonates.[1 2]

In treating the neonate with respiratory problems an arterial oxygen tension of 8–12 kPa is considered optimal. Surfactant therapy can cause an initial surge in oxygenation to levels of 20–30 kPa which is now closely monitored by pulse oximetry so that supplemental oxygen is reduced optimising tissue oxygenation and so avoiding the risks of hyperoxaemia.

The population of surfactant treated babies described in this study had severe RDS and were treated in a 'rescue' rather than a prophylactic trial. The comparison group did not have severe RDS and therefore were generally a less sick population. The results should be viewed with this disparity in mind so that the original hypothesis that there may be an increased risk of ROP in the sicker population requiring surfactant treatment was not sustained.

Estimates of the incidence of ROP in similar age and birthweight matched populations vary from 3–50%.[8 9] Our rates of 25·9% in the surfactant group and 17·8% in the comparisons are therefore compatible. It is perhaps more relevant to study how many infants progress to threshold disease as this is the group in whom intervention with cryopexy is indicated.[10] Only 1·7% of the surfactant group and 7·8% of comparisons reached threshold disease or greater and in the most at-risk population of less than 1000 g birth weight the incidence is 4% in the surfactant group and 16·3% in the comparisons. These differences are not significant but they confirm that despite being a sicker more at risk population babies receiving surfactant are not at increased risk of ROP.

Kalina has recently highlighted the concern that the increased survival of low birthweight infants and their prolonged oxygen dependence may increase their risk of ROP.[11] It is our view that decreasing the severity of the early insult will decrease the risk of severe ROP. The value of surfactant therapy is not only in improving the survival of low birthweight infants but also decreasing the risk of severe ROP.

By improving oxygenation and stabilising infants' homeostasis in this early critical period subsequent prolonged oxygen dependence may not be as significant a factor in the genesis of ROP. Surfactant replacement therapy may have an important role in achieving this early stability. Further investigation is warranted to increase the numbers of infants treated with different types of surfactant and examined for ROP so that any potential beneficial effect can be confirmed.

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British Journal of Ophthalmology, 1992, **76**, 205–209

In situ immunohistochemical analysis of cell adhesion molecules on human corneal endothelial cells

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Abstract

Interaction of leucocytes with human corneal endothelial cells (HCECs) can be observed in several clinicopathological conditions, such as uveitis, keratitis, and corneal graft rejection. Since leucocyte-endothelial cell interactions involve various adhesion receptors we have analysed the expression and distribution pattern of the neural cell adhesion molecule (NCAM), the intercellular adhesion molecule-1 (ICAM-1), the vascular cell adhesion molecule-1 (VCAM-1), the endothelial leucocyte adhesion molecule-1 (ELAM-1), and the cluster of differentiation antigen-44 (CD44) on flat preparations of normal and organ-cultured HCECs. NCAM and ICAM were constitutively expressed on HCECs whereas VCAM-1, ELAM-1, and CD44 were absent from normal HCECs. However flat mounts of HCECs from organ-culture preserved corneas showed a mosaic-like distribution pattern of VCAM-1 and ELAM-1 positive cells and garland-like clusters of CD44 positive cells. We suggest that modulation of ELAM-1, VCAM-1, and CD44 expression on HCECs may contribute to the regulation of leucocytes-HCECs interaction in the case of anterior segment inflammation.

In a variety of ocular clinicopathological conditions interactions of human corneal endothelial cells (HCECs) with leucocytes can be observed with the slit-lamp. Clusters of inflammatory cells deposited on the inner surface of the cornea from the aqueous humour and known as keratic precipitates are seen in conditions of anterior segment inflammation – that is, keratitis and/or anterior uveitis.[1] In particular T lymphocytes are thought to play a crucial role in mediating the local reaction against the corneal endothelium in corneal allograft rejection.[2 3 4] Clinically endothelial immunoreaction is characterised by diffusely spread keratic precipitates or by a Khodadoust line migrating over the graft endothelium.[5 6]

In the past few years cell adhesion molecules which mediate interaction between leucocytes and various target cells have been extensively investigated.[7–13] In addition to the intercellular adhesion molecule-1 (ICAM-1)[14 15] two other vascular cell adhesion molecules involved in leucocyte trafficking have recently been described – that is, the endothelial-leucocyte adhesion molecule-1 (ELAM-1),[16 17] and the vascular cell adhesion molecule-1 (VCAM-1).[18] The cluster of differentiation antigen-44 (CD44) involved in lymphocyte recognition of high endothelial venules probably represents a novel type of cell adhesion molecule mediating cell-cell or cell-matrix interaction in multiple tissues.[19] In spite of these recent advances in basic immunology the mechanisms which regulate interactions between leucocytes and HCECs during anterior segment inflammation are virtually unknown.

We therefore wanted to identify cell adhesion molecules which might be involved in leucocytes-HCECs interactions; for this purpose we used in situ immunoperoxidase staining techniques and a panel of monoclonal antibodies to determine the expression and distribution of various adhesion molecules on flat mounts of HCECs. We chose to use flat mounts of HCEC-Descemet's membrane complexes to overcome the damage to and loss of HCECs in frozen tissue sections and because this method has previously shown heterogeneity among HCECs.[20 21]

Material and methods

We studied the endothelium of seven corneoscleral rims (specimens 1–7), obtained following trephination of donor corneas at the time of keratoplasty. These donor corneas were derived from the Leuven Eye Bank.[22] The corneas were excised 9–22 h post mortem from human cadaver eyes (age 47–79, mean 67) and were stored for various intervals (8–26 days, mean 18 days) in Minimum Essential Medium (Gibco, Paisley, Scotland) supplemented with 10% fetal calf serum (Gibco), 50 U/ml nystatin, 0·1 mg/ml amikacin, and 0·5 mg/ml ticarcillin at 32°C. The viability of the corneal endothelial cell layer was evaluated by vital staining with Evans' blue.

Each corneal specimen was cut into several pieces and Descemet's membrane with the covering endothelial cell layer was gently stripped off from the underlying stroma using fine monofilament forceps.[23] The samples of Descemet's membrane-endothelium complex were mounted on albumin-coated slides, dried overnight at room temperature, and fixed for 10 minutes in absolute acetone.

To study the effect of organ culture medium the endothelium of four human cadaver corneas (specimens 8–11), which were not preserved in medium, was treated in the same way. Age of the donors was 77, 67, 67, and 44 years and postmortem enucleation time was 6, 9, 16, and 24 hours respectively.

One cornea (specimen 12) from an eye enucleated because of primary malignant melanoma of the choroid (the patient was 70 years old) was divided into three parts. The endothelium of one part was peeled off

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Accepted for publication 22 August 1991

immediately after enucleation. The remaining two pieces were put in organ culture medium respectively during 5 and 10 days before the endothelium was stipped off.

Finally two diseased corneal buttons (specimens 13 and 14) with centrally perforated ulcer obtained at keratoplasty were included in the study. The Descemet's membrane with remaining endothelial cells was peeled off from the diseased corneal stroma and handled in the same manner.

Table 1 Monoclonal antibodies used in this study

Specificity (Refs)	*Clone*	*Working dilution*	*Source*
ICAM-1 (24)	84H10	1:50	Serotec
NCAM (25)	Leu19	1:160	Becton Dickinson
VCAM-1 (26)	4B9	1:10	Dr T Carlos
VCAM-1 (27)	E1/6	1:10	Dr M P Bevilacqua
VCAM-1 (28)	2G7	1:100	Dr W Newman
ELAM-1 (16)	H18/7	1:250	Dr M Gimbrone
ELAM-1 (16)	H4/18	1:250	Dr M Gimbrone
CD44 (29)	F10-44-2	1:100	Dr R Dalchau
CD44 (30)	NIH44-1	1:1000	Dr Y Shimizu
CD44 (12)	A3D8	1:1000	Dr B F Haynes
CD44 (31)	Hermes-3	1:500	Dr S Jalkanen

Table 2 Expression of adhesion molecules of flat mounts of HCECs

	Fresh cornea	*Organ culture preserved cornea*	*Inflamed cornea*
ICAM-1	diffusely +	diffusely +	diffusely +
NCAM	diffusely +	diffusely +	diffusely +
VCAM-1	–	scattered +	scattered +
ELAM-1	–	scattered +	not demonstrated
CD44	–	garland-like clusters	diffusely +

Adhesion molecules were demonstrated by an avidin-biotin-peroxidase complex (ABC) method. Slides mounted with Descemet's membrane-endothelium complex were incubated with mouse monoclonal antibody listed in Table I. The optimal dilution of each antibody was determined by titration experiments on positive controls. The secondary antibody consisted of biotinylated rabbit-antimouse Ig, and the third step consisted of the avidin-biotin-peroxidase complex. All incubations were carried out at room temperature for 30 minutes, and followed by a 15-minute wash in three changes of phosphate-buffered saline (PBS), pH 7·2. Peroxidase activity was developed with the use of 3-amino-9-ethylcarbazole and H_2O_2 resulting in a brightly red colour of immunoreactive sites. After a final wash in PBS, pH 7·2, the sections were slightly counterstained with Harris' haematoxylin. Controls consisted of replacement of the primary monoclonal antibody by an irrelevant antibody of similar isotype or by PBS, pH 7·2. These controls were invariably negative.

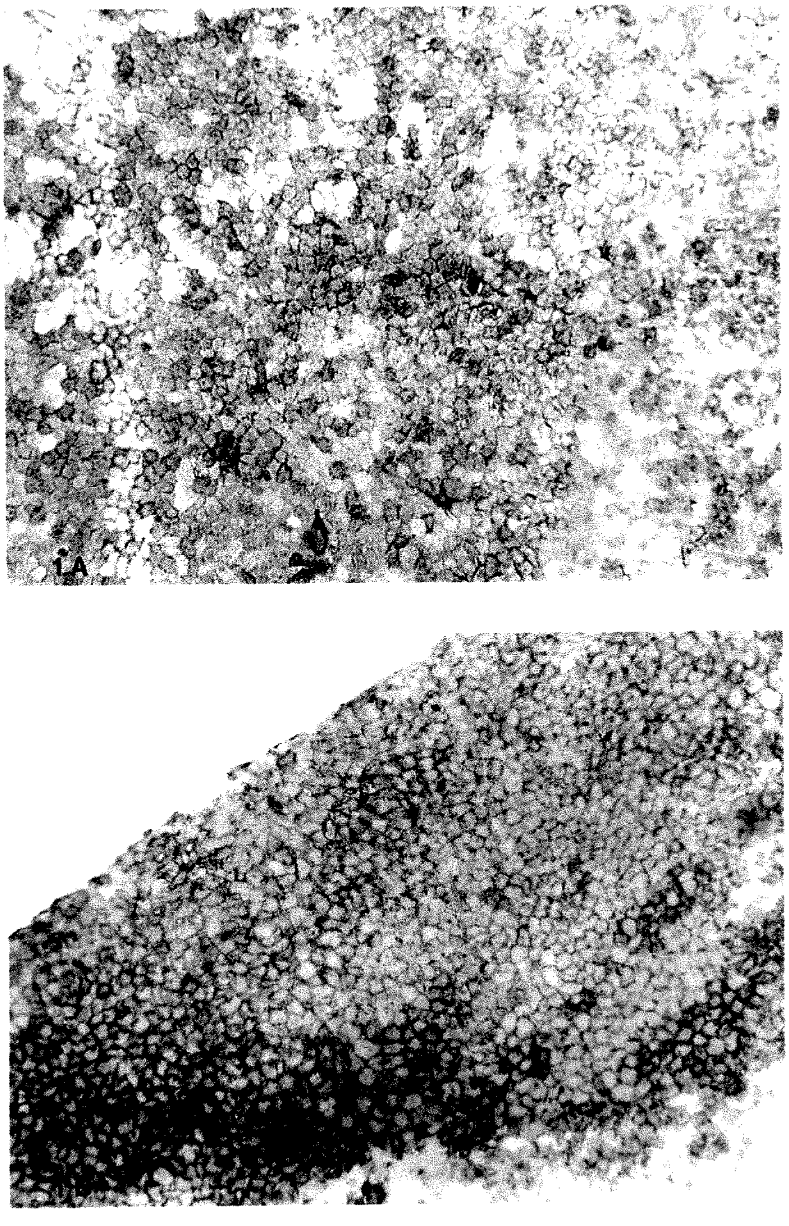


Figure 1 Staining of HCECs from organ culture preserved corneas with monoclonal antibodies against ICAM-1 (A), NCAM (B), VCAM-1 (C) and ELAM-1 (D). HCECs diffusely display immunoreactivity for ICAM-1 and NCAM. Expression of VCAM-1 and ELAM-1 is found on scattered endothelial cells of preserved corneas. Three-step indirect immunoperoxidase, counterstained with Harris' haematoxylin; original magnification: ×45.

Results

The distribution of NCAM, ICAM-1, VCAM-1, ELAM-1, and CD44 on HCECs of fresh, organ culture preserved and diseased corneas is summarised in Table 2.

ICAM-1 and NCAM were diffusely expressed on all HCECs of organ culture preserved and fresh corneas (Figs 1A and B).

Monoclonal antibodies 4B9, E1/6, and 2G7, all directed to VCAM-1, gave identical staining results. With the exception of one corneal specimen corneal endothelial cells from freshly prepared corneas (specimens 8-12) did not express VCAM-1. However HCECs from organ culture preserved corneas consistently showed variable numbers of VCAM-1 positive cells scattered between VCAM-1 negative endothelial cells (Fig 1C). This mosaic pattern was present both in the centre and periphery of the cornea, and there was no relationship between the number of positive cells and the incubation time in the culture medium.

Monoclonal antibodies H18/7 and H4/18 both detecting ELAM-1 yielded similar staining patterns. ELAM-1 could not be identified on a fresh corneal specimen but was expressed on scattered endothelial cells derived from two preserved corneal rims (Fig 1D).

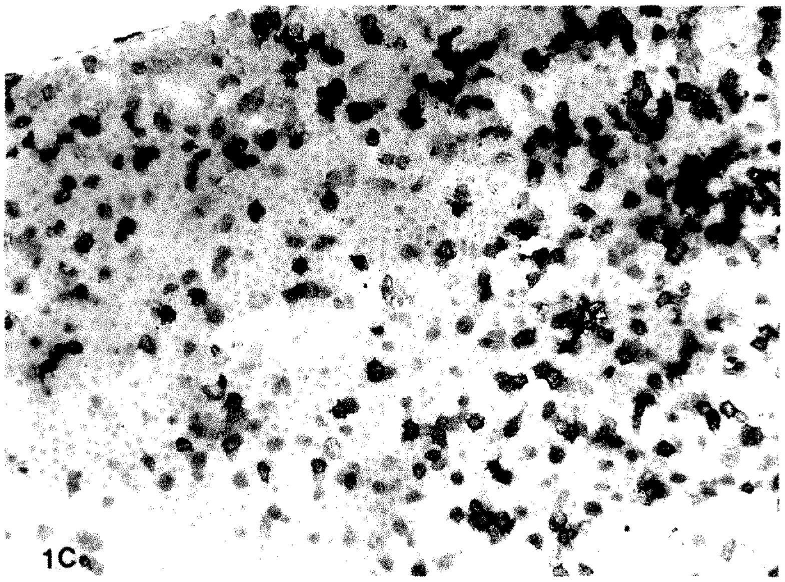
All four anti-CD44 monoclonal antibodies (F10-44-2, NIH44-1, A3D8, and Hermes-3) gave similar staining results. The CD44 molecule could not be detected on fresh corneal endothelial cells (Fig 2A). Flat mounts of HCECs derived from organ culture preserved corneas on the other hand showed remarkable garland-like clusters of CD44 positive cells (Figs 2B and C).

The endothelial cells of the two diseased corneal buttons (specimens 13-14) were diffusely CD44 positive. On one of the diseased buttons VCAM-1 positive HCECs were present.

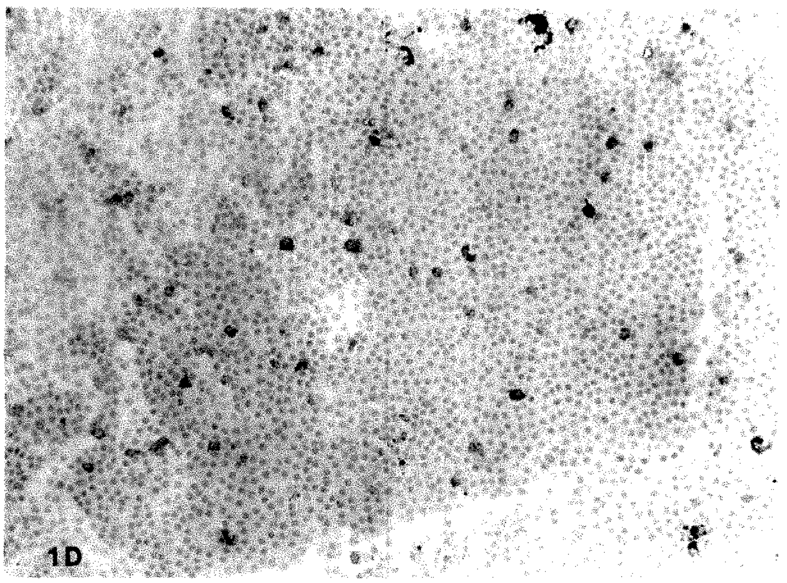
Discussion

In the present study we have analysed the expression and distribution pattern of the adhesion molecules NCAM, ICAM-1, VCAM-1, ELAM-1, and the lymphocyte homing-receptor CD44 using in situ immunohistochemical techniques on flat preparations of HCECs.

NCAM and ICAM-1 are both relatively well characterised members of the immunoglobulin gene superfamily of adhesion molecules.[32] They are similar in overall structure since each is an integral membrane glycoprotein constructed from five immunoglobulin-like domains forming the N-terminal extracellular region.



1C



1D

NCAM mediates neuron-neuron and neuron-muscular adhesion through homophilic NCAM-NCAM interactions.[33] In addition NCAM has been shown to be involved in cell-matrix interactions.[34] In adult life expression of NCAM is restricted to neural tissues and endocrine cells,[33 35] and the constitutive expression of NCAM by HCECs is in line with their neural crest origin.[20 36] Further studies will have to disclose whether NCAM serves in the adhesion of HCECs to each other or in the adhesion of these cells to matrix components of Descemet's membrane.

ICAM-1 is expressed on many cell types both of non-haematopoietic and haematopoietic lineage,[14 15] and has been identified as a ligand for the LFA-1 molecule,[37 38] one of a trio of heterodimeric molecules known as the β_2 – or leucocyte – integrins present on virtually all leucocytes.[11] In analogy with a recent report,[39] HCECs were found to express ICAM-1 constitutively. Thus HCECs can serve as a cell type with which lymphocytes in the anterior eye chamber can interact via the ICAM-1/LFA-1 adhesion pathway a feature that has been proved recently by a leucocyte adherence assay using cultured HCECs.[39]

Recently two inducible vascular adhesion molecules have been identified – VCAM-1 and ELAM-1. VCAM-1 also belongs to the immunoglobulin gene superfamily of adhesion molecules and is induced by the cytokines IL1 and TNF-α on the surface of vascular endothelial cells.[18 27] VLA-4 a member of the β_1-integrin subfamily and primarily expressed on lymphocytes and monocytes,[40] has recently been shown to be the major ligand for VCAM-1.[41] ELAM-1 is a member of a new family of adhesion proteins called selectins.[7 8] These adhesion proteins have lectin-like domains on their outermost end suggesting that they recognise and bind to carbohydrates. ELAM-1 appears on the endothelium of blood vessels that have been stimulated by inflammatory cytokines and attracts neutrophils to inflamed areas.[16 17 42]

VCAM-1 and ELAM-1 are absent from normal corneal endothelial cells. Unexpectedly however a mosaic-like expression of both vascular cell adhesion proteins was observed on flat preparations of HCECs from organ culture preserved corneas indicating induction of these molecules by a hitherto unknown component in the medium. Negative control experiments excluded the possibility that this patchy distribution was due to passive uptake of the antibody by necrotic HCECs. The observed heterogeneous expression of VCAM-1 and ELAM-1 on HCECs triggered by components in the culture medium adds to our previous demonstration of phenotypic heterogeneity among HCECs with regard to their intermediate filament make-up,[20] their affinity for the lectin Ulex Europaeus Agglutinin I[43] and their expression of MHC class II antigens in response to cytokines.[21] The presence of VCAM-1 and ELAM-1 on a subset of HCECs does not necessarily indicate their vascular endothelial nature; the recent demonstration of VCAM-1 staining of inflamed mesothelium,[44]

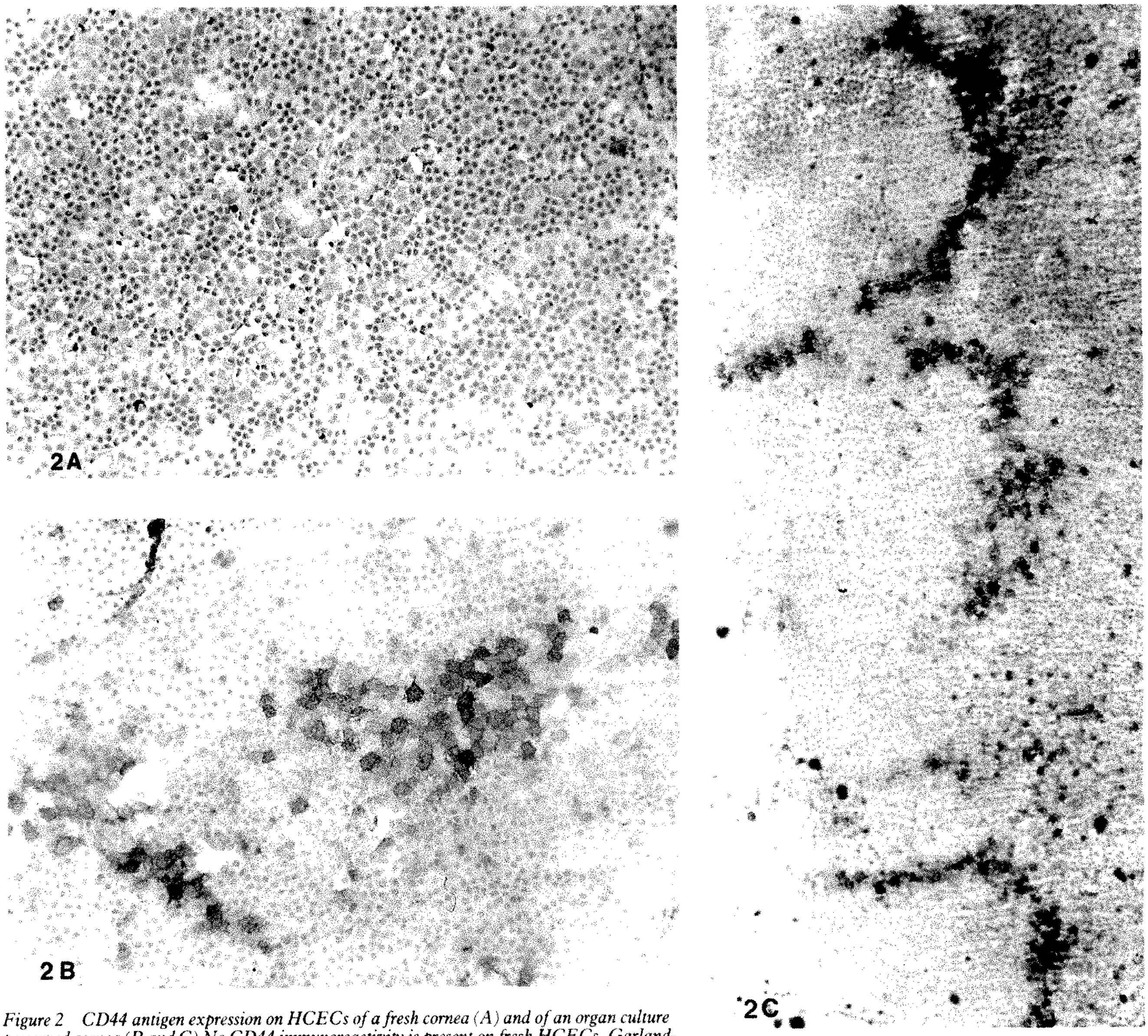


Figure 2 CD44 antigen expression on HCECs of a fresh cornea (A) and of an organ culture preserved cornea (B and C) No CD44 immunoreactivity is present on fresh HCECs. Garland-like clusters of CD44 positive HCECs are seen on flat mounts of HCECs from organ culture preserved corneas. Three-step indirect immunoperoxidase, counterstained with Harris' haematoxylin; original magnification: ×45 (A and B), and ×36 (C).

together with the previous demonstration of cytokeratin filaments in HCECs,[20] would rather support their mesothelial nature.

The present data indicate that HCECs can express the cytokine-inducible adhesion molecules VCAM-1 and ELAM-1. It is therefore conceivable that inflammatory cytokines, which undoubtedly circulate in vivo during an inflammatory reaction, may induce expression of ELAM-1 and/or VCAM-1 on HCECs thereby promoting adherence of leucocytes to the corneal endothelium. This needs to be proved by in vitro studies adding various cytokines to the culture medium of the corneas as well as by monoclonal antibody blocking studies. It is tempting to speculate that the observed patchy distribution of adhesion molecules on HCECs occurs also in vivo during anterior segment inflammation and that this represent the molecular basis for the spotty configuration of keratic precipitates observed with the slit-lamp.

CD44 is a widely expressed membrane glycoprotein that exists in a variety of structural forms the most common of which has a molecular weight of approximately 90 kDa.[19,45,46] CD44, homologous to the cartilage link protein family,[47] has been implicated in the adhesion of lymphocytes to high endothelial venules and in the trafficking of leucocytes to sites of tissue inflammation; in addition CD44 would serve as a receptor for components of the extracellular matrix.[48] The wide distribution of the CD44 molecule on various cell types suggests that it is a general adhesion molecule mediating interaction among many cell types. CD44 is not expressed by normal HCECs but a peculiar garland-like distribution of CD44-positive cells was seen on flat preparations of HCECs from organ cultured corneas. In addition HCECs on the inflamed corneal specimens were diffusily CD44 positive. We suggest that CD44 represents an HCEC-inducible surface protein the expression of which confers new functional properties to HCECs in cases of inflammatory conditions. In the context of corneal transplantation immunobiology inflammatory cytokines are released during anterior chamber irritation; the upregulation of CD44 in addition to the induction of MHC class II antigens at the surface of transplanted corneal endothelial cells may promote the afferent phase of the immune reaction via stimulation of T helper cells. The peculiar distribution in garland-like sheets of CD44 positive cells may signify a hitherto unrecognised compartmentalisation of HCECs.

Dr M Gimbrone (Harvard Medical School, Boston, USA), Dr T Carlos (Harborview Medical Center, Seattle, USA), Dr M P Bevilacqua (Harvard Medical School, Boston, USA), Dr W Newman (Otsuka America Pharmaceutical, Rockville, USA), Dr R Dalchau (Blond McIndoe Center for Medical Research, East Grinstead, Dr Y Shimizu (National Institute of Health, Bethesda, USA), Dr S Jalkanen (Turku University, Finland), Dr B F Haynes (Duke University Medical Center, Durham, USA) are acknowledged for their generous gifts of monoclonal antibodies.

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British Journal of Ophthalmology, 1992, 76, 210–213

Localisation of prostaglandin $F_{2\alpha}$ and E_2 binding sites in the human eye

Toshihiko Matsuo, Max S Cynader

Abstract

Prostaglandin $F_{2\alpha}$ reduces intraocular pressure possibly by increasing uveoscleral outflow. To further understand the mechanism of its action binding sites for prostaglandin $F_{2\alpha}$ and, for comparison, prostaglandin E_2 were localised in sections of human cadaveric eyes using an in vitro ligand-binding technique and autoradiography. Specific binding sites for both prostaglandin $F_{2\alpha}$ and E_2 were co-localised at a high level in the areas of the ciliary muscles and iris sphincter muscles, and at a lower level in the iris epithelium and the retina. The results suggest that prostaglandin $F_{2\alpha}$ and also prostaglandin E_2, could modulate uveoscleral outflow by binding to their receptors located on the ciliary muscles and inducing their relaxation.

Prostaglandin $F_{2\alpha}$ and especially its more lipophilic prodrug prostaglandin $F_{2\alpha}$-1-isopropylester can reduce intraocular pressure (IOP) when applied topically to normal human volunteers[1 2 3] and patients with glaucoma.[4 5] Prostaglandin $F_{2\alpha}$ isopropylester is a very promising drug for glaucoma treatment because it has a prolonged potent hypotensive effect in low doses and lacks serious subjective or objective side effects.

A working classification of prostanoid receptors for five naturally occurring prostaglandins has been proposed based on pharmacological studies in which the agonist potencies of naturally occurring prostaglandins as well as other synthetic agonists and antagonists were compared.[6 7] Receptors sensitive to thromboxane A_2, prostaglandin D_2, E_2, $F_{2\alpha}$, and I_2 have been designated as TP, DP, EP, FP, and IP-receptors, respectively. The EP receptor can be further classified into three subtypes, called EP_1, EP_2, and EP_3 receptors.[8 9] The EP_3 receptor has been shown to be involved in reduction of IOP in rabbits.[10 11] However it is not known which class of prostanoid receptors is involved in the pressure reduction for humans and where within human eyes the receptors for prostaglandin $F_{2\alpha}$ are located.

There is evidence that prostaglandin $F_{2\alpha}$ lowers IOP by increasing uveoscleral outflow in monkeys.[12-14] In order to further understand the basic mechanism of its action it is crucial to reveal the localisation of binding sites (receptors) for prostaglandin $F_{2\alpha}$ in the eye. It is also important to use human eyes since there are considerable anatomical and physiological differences between the eyes of different species, especially in the systems controlling aqueous humour outflow.[15] In this study we localised binding sites for prostaglandin $F_{2\alpha}$ and also for prostaglandin E_2 in human eye sections using an in vitro ligand binding technique and autoradiography.

Materials and methods

PREPARATION OF HUMAN EYE SECTIONS

Human cadaveric eyes were obtained within 24 hours after death from the Eye Bank of British Columbia. The eyes used in this study had no documented ocular diseases. They were frozen in isopentane cooled to −80°C and stored at −20°C until use. Sections of 20 µm thickness were cut with a cryostat (Cambridge Instruments, Nussloch, Germany) and placed on glass slides coated with 1·7% gelatin.

IN VITRO LIGAND BINDING AND AUTORADIOGRAPHY

The sections were thawed at room temperature and preincubated in 50 mM tris-hydrochloride buffer (pH 7·4) containing 100 mM sodium chloride, 3 mM calcium chloride, and 5% (weight/volume) bovine serum albumin (BSA, Sigma, St Louis, MO, USA) for 60 minutes at room temperature. The sections were then incubated in the same buffer containing 10–20 nM of tritiated prostaglandin $F_{2\alpha}$ or E_2 (Du Pont Canada, Mississauga, Ontario) for 90 minutes at room temperature, washed for 60 minutes in the ice-cold buffer containing 1% BSA, and finally dried in an air stream. The sections were then apposed to tritium-sensitive films (Hyperfilm-^{3}H: Amersham Canada, Oakville, Ontario) for 8 weeks in the dark. Non-specific binding was determined by incubating sections in the buffer containing, in addition, 100 µM unlabelled prostaglandin $F_{2\alpha}$ or prostaglandin E_2 (Cayman Chemicals, Ann Arbor, MI, USA) as well as 10–20 nM of a labelled ligand.

Results

Specific binding sites for both prostaglandin $F_{2\alpha}$ and E_2 were co-localised in the areas of the ciliary muscles and iris sphincter muscles at a high level, and also in the iris epithelium and the retina at a lower level as shown in Figures 1 and 2. The lens structure showed apparently moderate levels of the binding for both prostaglandins, which were not distinctive compared with levels of the corresponding non-specific binding. The results were reproducible in three eyes from three different individuals: a 60-year-old man who died of cerebral infarction, a 70-year-old woman who died of myocardial infarction, and a 52-year-old woman who died of colon cancer.

The binding of 20 nM tritiated prostaglandin $F_{2\alpha}$ in all of the areas could be totally displaced by

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Accepted for publication
6 September 1991

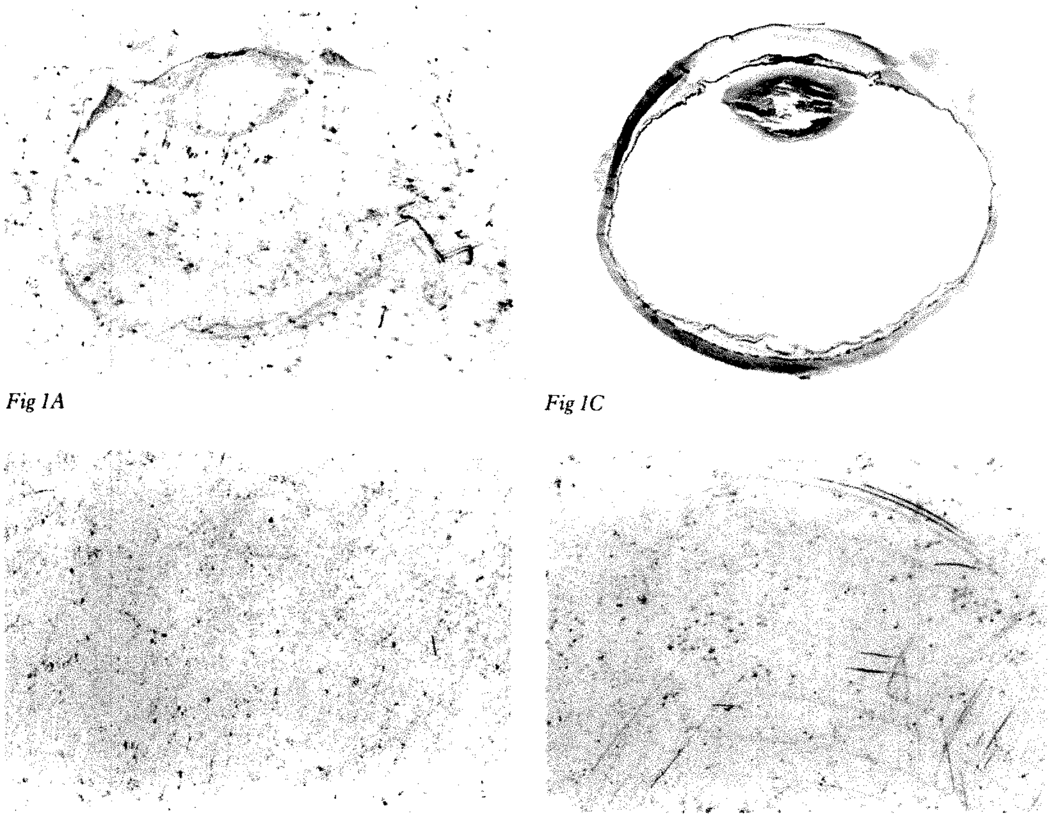

Fig 1A

Fig 1C

Fig 1B

Fig 1D

Figure 1 Autoradiographic views of prostaglandin $F_{2\alpha}$ binding sites in eye sections from a 60-year-old man. The binding of 20 nM tritiated prostaglandin $F_{2\alpha}$ (A) concentrates in the ciliary muscle, iris sphincter muscle, iris epithelium, and the retina (and the detached retina). The binding was completely displaced by 100 μM unlabelled prostaglandin E_2 (B) and by 100 μM unlabelled prostaglandin $F_{2\alpha}$ (D). A Nissl-stained view of A is given in C.

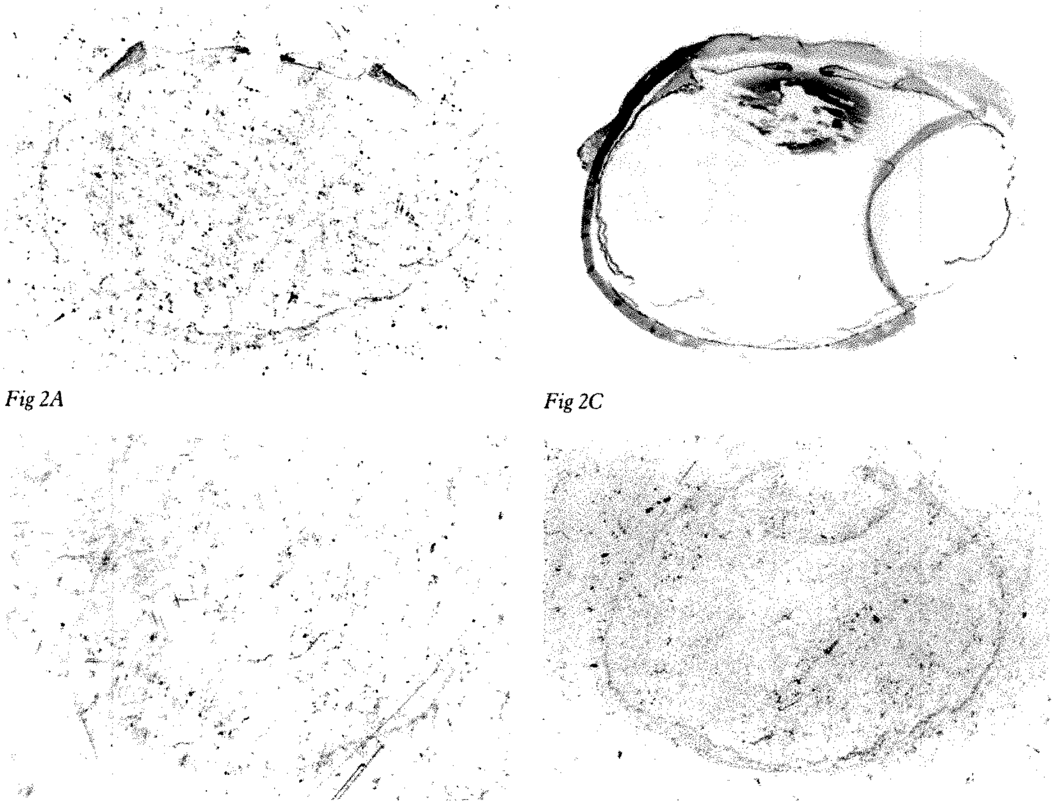

Fig 2A

Fig 2C

Fig 2B

Fig 2D

Figure 2 Autoradiographic views of prostaglandin E_2 binding sites in eye sections from a 60-year-old man. The binding of 20 nM tritiated prostaglandin E_2 (A) concentrates in the ciliary muscle, iris sphincter muscle, iris epithelium, and the retina (and the detached retina). The binding was completely displaced by 100 μM unlabelled prostaglandin E_2 (B), and partially displaced by 100 μM unlabelled prostagladin $F_{2\alpha}$ (D). A Nissl stained view of A is given in C.

100 μM unlabelled prostaglandin $F_{2\alpha}$ and prostaglandin E_2 as shown in Figure 1. The binding of 20 nM tritiated prostaglandin E_2 could be totally displaced by 100 μM unlabelled prostaglandin E_2, and partially and evenly in every area by 100 μM prostaglandin $F_{2\alpha}$ as shown in Figure 2.

Retinal detachment commonly resulted during the processing of the eyes of autoradiography. This separated the retina from other layers in the posterior segment and made it clear that specific binding sites for prostaglandin $F_{2\alpha}$ and E_2 in the posterior segment were located mainly in the retina with minimal density in the choroid and retinal pigment epithelial cells. The resolution of the autoradiographic films was insufficient to determine which specific layer in the retina, if any, showed a high concentration of prostaglandin binding sites.

Discussion

Prostaglandins are known to bind with pigments in the eye tissues.[16] In the present experiments the binding of prostaglandins to pigments could be reduced to less than 10% of the total binding by preincubating and incubating the sections with high concentrations (5%) of BSA and washing the sections with 1% BSA for durations as long as 60 minutes. The conditions used are based on the fact that prostaglandins are lipophilic and bind to the pigments with a weaker affinity than they do to their receptors.

In the present experiments, binding sites for prostaglandin $F_{2\alpha}$ and prostaglandin E_2 were colocalised to the same areas of the eye, primarily the ciliary muscles and iris sphincter muscles, the iris epithelium, and the retina. The results indicate that these areas had a mixture of binding sites (receptors) for both prostaglandins. However both prostaglandins can bind to the EP and FP prostanoid receptors at the ligand concentrations used in the experiments.[6-11] Further reduction of the ligand concentration to try to elicit more specific binding led to an inability to visualise any binding sites. This failure is due to the limited resolution of the autoradiographic techniques and to a relatively high noise/signal ratio caused by the high 'background' binding of prostaglandins to the ocular pigments as mentioned above.

The binding of prostaglandin $F_{2\alpha}$ was totally displaced by prostaglandin E_2, whereas the binding of prostaglandin E_2 was not totally displaced by prostaglandin $F_{2\alpha}$. These results indicated that most of the binding sites were receptive to both prostaglandin $F_{2\alpha}$ and E_2 at the 20 nM concentrations, whereas there were some binding sites receptive only to prostaglandin E_2 at that concentration. Thus the binding sites detected in this study would be a mixture of heterogeneous types (EP receptors and FP receptors) and subtypes (those of EP receptors) of the prostanoid receptors.

The reduction of IOP by prostaglandins has been previously demonstrated to be mediated by stimulation of the EP_3 prostanoid receptor but not of the FP receptor in rabbits.[10 11] It is still unknown which specific class of prostanoid receptors is involved in the pressure reduction induced by prostaglandin $F_{2\alpha}$ in human eyes. The present experiments suggest that the ciliary muscles in human eyes have both EP receptors and FP receptors. Further studies using more specific and sensitive ligands not presently available are required to answer the question of which specific class of prostanoid receptors plays the most important role in ocular hypotension.

Prostaglandin $F_{2\alpha}$ did not change the production of aqueous humour by the ciliary epithelial cells,[17 18] nor did it facilitate conventional outflow through the trabecular meshwork in humans[4 17] or monkeys.[19] Instead prostaglandin $F_{2\alpha}$ apparently enhanced uveoscleral outflow in monkeys[12 13] and its pressure-lowering effect was antagonised by pilocarpine.[14] However the exact mechanism by which it modulates the uveoscleral outflow remains unknown. Uveoscleral outflow can be affected by the tone of the ciliary muscles: contraction of the muscles induced by pilocarpine reduces the uveoscleral flow whereas their relaxation by atropine enhances the flow.[20 21] The binding sites for prostaglandin $F_{2\alpha}$ appeared to be localised along bundles of the ciliary muscle in the ciliary body. It is therefore most probable that receptors for prostaglandin $F_{2\alpha}$ are located on the ciliary muscles.

Repeated doses of prostaglandin $F_{2\alpha}$ produced narrowing of the ciliary muscle fibres and widening of the intermuscular spaces in cynomolgus monkeys[22] and might also cause lysis and loss of intermuscular connective tissue.[23] Its administration was accompanied by partial reversal of resting myopia in monkeys[24] but it did not induce any measurable refractive changes in humans.[3 4]

Although the facts mentioned above suggest that prostaglandin $F_{2\alpha}$ could induce relaxation of the ciliary muscles there has been no evidence as to how prostaglandins would act directly on ciliary muscles, whether they induce contraction or relaxation of the muscles, or whether they act in a completely different way. Recently, prostaglandin E_2 (most potent), D_2 and $F_{2\alpha}$ (less potent) were reported to induce relaxation of the isolated longitudinal ciliary muscles of cats which had been contracted beforehand with carbachol.[25] The autoradiographic techniques used here also demonstrated that the ciliary muscle in cats had binding sites for prostaglandin $F_{2\alpha}$ and E_2 as did in humans (data not shown). It will be necessary to examine further the direct effect of prostaglandins on the ciliary muscle, especially in humans, to fully solve these questions.

Prostaglandin E_2 and $F_{2\alpha}$ can be synthesised by cells lining the trabecular meshwork in humans.[26 27] These prostaglandins would remain active for a while until they flow or are transported out of the eye,[28 29] since ocular tissues in humans so far examined apparently do not contain enzymes which degrade prostaglandins metabolically.[30] The present results support the idea that prostaglandins synthesised in the trabecular meshwork would flow posteriorly in the aqueous humour and reach the ciliary body where they may modulate uveoscleral outflow consequent to binding to their receptors located on the ciliary muscle. Of course there is another possibility, namely, that the ciliary muscle itself might synthesise prostaglandins under certain conditions and thus might, in effect, turn on the uveoscleral outflow pathway.

The fact that the iris sphincter muscles had binding sites for prostaglandin $F_{2\alpha}$ and E_2 suggests that both prostaglandins might induce miosis although miosis caused by their topical administration has not yet been confirmed clinically.[31]

Prostaglandins play a role in the development of cystoid macular oedema especially after cataract extraction.[32] Binding sites for prostaglandin $F_{2\alpha}$ and E_2 found in the retina might support the role of these compounds in cystoid macular oedema. Prostaglandins are known to be actively transported out of the intraocular fluids by an organic acid transport system located in the ciliary epithelium and retinal capillaries.[28,29] Therefore there is a possibility that some of the binding sites detected in the retina by the ligand-binding method would be the sites of this transporter. This result also suggests a possibility that prostaglandin $F_{2\alpha}$ and E_2 could play roles as retinal neuromodulators as has been shown in the brain.[33]

Receptor proteins for prostaglandin E_2 and $F_{2\alpha}$ have been solubilised and shown to be coupled with guanine nucleotide binding proteins (G proteins).[34] Recently a gene for the human thromboxane A_2 receptor has been cloned and shown to belong to the superfamily of G protein-coupled receptor proteins. Expression of this cloned gene for thromboxane A_2 revealed that the receptor responded only to thromboxane A_2 agonists but not to prostaglandin D_2 or $F_{2\alpha}$, supporting the working hypothesis that there might be a separate receptor for each of the naturally occurring prostanoids. In the future molecular biological approaches will further enhance our understanding of the action of prostaglandins in ocular tissues.

This work was supported by a MRC fellowship to TM and by grants from Allergan Pharmaceutical Co Ltd, Irvine, CA, USA.

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British Journal of Ophthalmology, 1992, 76, 214–217

PhXA34 – a prostaglandin $F_{2\alpha}$ analogue. Effect on intraocular pressure in patients with ocular hypertension

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Accepted for publication
3 October 1991

Abstract

PhXA34, a prostaglandin analogue, was given topically to 40 patients with untreated ocular hypertension in a double masked randomised study. One single dose of 0·3, 1, 3, 10 μg, or placebo (vehicle) was given to one eye of each patient. A dose related IOP reduction ranging from 11 to 35% was observed with a maximal effect with 3 and 10 μg PhXA34. No hyperaemia was seen except after 10 μg PhXA34, where a mild to moderate hyperaemia was seen from 8 hours with a duration of up to 24 hours. Mild foreign body sensation in the PhXA34-treated eye was noted by three patients. No cells or flare were seen.

Topical prostaglandin $F_{2\alpha}$-isopropylester ($PGF_{2\alpha}$-IE) reduces the intraocular pressure (IOP) both in normal and glaucomatous human eyes,[1-5] but side effects such as hyperaemia and discomfort are observed even after doses of $PGF_{2\alpha}$-IE at the low range of the dose-response curve. An analogue of $PGF_{2\alpha}$-IE, 13, 14-dihydro-15 (R,S)-17-phenyl-18, 19, 20-trinor $PGF_{2\alpha}$-IE (PhXA34), is a potent ocular hypotensive agent in healthy eyes of young volunteers, and only minor side effects were observed after high doses.[6] Thus PhXA34 improves the effect/side effect relationship compared with the parent compound $PGF_{2\alpha}$-IE. The present report aims to study the dose-response with regard to IOP reduction and side effects of PhXA34 in a group of eyes with elevated IOP.

Design

The study was a double-masked and, placebo controlled in which one eye of 40 patients was randomised to one of five treatments: 0·3 μg, 1 μg, 3 μg, 10 μg PhXA34 or placebo (vehicle). There were eight patients in each group. The contralateral eyes did not receive any treatment but were otherwise subjected to the same procedures as the study eyes. The study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty, University of Umeå and by the National Swedish Board of Health and Welfare. A signed informed consent was obtained from each patient.

PATIENTS

Patients were selected at the glaucoma unit of the Department of Ophthalmology. Inclusion criteria were age 30 to 80 years and untreated ocular hypertension with IOP more than 21 mm Hg on at least two occasions at the outpatient glaucoma unit, normal optic disc, normal visual field, and normal open anterior chamber angle. If both eyes were eligible the eye with the higher IOP was chosen. Excluded were patients who received any medication known to affect the IOP and patients with any pulmonary, cardiovascular, metabolic, or other systemic disease judged by the investigator to be reason for exclusion. Also excluded were patients with ocular infection or inflammation active within 3 months, any corneal abnormality preventing reliable applanation tonometry, previous treatment with topical cholinomimetics, and any past intraocular operation including argon laser trabeculoplasty. Women with child-bearing potential were included only if reliable birth control was used: 32 women aged 41 to 78 years, and eight men aged 56 to 73 years were included.

STUDY DRUGS

The test solutions were administered from dropper bottles with a drop size of approximately 35 μl. The vehicle contained polysorbate 80 (1·5 mg/ml) and benzalkonium chloride (0·2 mg/ml) in a phosphate buffer.

EXAMINATION SCHEDULE

The study was a single dose study carried out during 3 succeeding days with the last examination in the morning on day 3.

Day 1 (pretreatment day). A routine ocular examination including the optic disc and anterior chamber angle was performed. No drug was given but IOP measurements and examinations of the anterior chamber were performed four times: 7 am (t_0), 3 pm (t_8), 7 pm (t_{12}) and the next morning at 7 am (t_{24}). Each time the patients were asked about local and systemic symptoms.

Day 2 (treatment day). The drug was given topically in the selected eye after the IOP reading in the morning. Examinations of anterior chamber, IOP measurements, and registration of symptoms were performed as on day 1 but also 30 minutes after drug administration. Before each examination during the treatment day en face photographs were taken of the eyes of the patients.

Methods

IOP

The IOP was measured with a Goldmann applanation tonometer in a masked fashion (the scale of the tonometer was masked to the examiner). Three measurements were taken from each eye always starting with the right eye. The median value of the three readings was taken as the true IOP.

HYPERAEMIA

The degree of hyperaemia was determined from colour photographs and graded on a scale from 0 to 3 with seven steps, by comparing with four standard photographs covering the range from none to pronounced hyperaemia. The average of four independent and masked gradings determined the hyperaemia.

CELLS AND FLARE

The anterior chamber was examined by slit-lamp biomicroscopy. Flare was graded none, slight, moderate, or severe, and the number of cells, if any, were counted.

SYMPTOMS

Prior to IOP measurements the patients were asked in a standardised way about local and systemic symptoms. Symptoms and discomfort were graded mild, moderate, or severe.

DATA ANALYSIS

All IOP values are presented as means with 95% confidence intervals. The IOP values used for the dose-response curve (Fig 1) are based on the IOP determinations at t_8 and t_{12}. These two IOP values were averaged and the difference between average IOP day 1 (before treatment) and day 2 (after treatment) has been used as an estimate of drug effect for each patient. Also the differences in IOP for corresponding examination times on day 1 and day 2 have been calculated for all doses including placebo (see Table 2).

To find statistically significant differences between placebo effect and drug effects non-paired t tests have been used. The effect on IOP expressed as the area under the curve for the differences in IOP day 1 and day 2 for each treatment group has been calculated using a simple numerical estimation of area by the trapezoidal rule.[7]

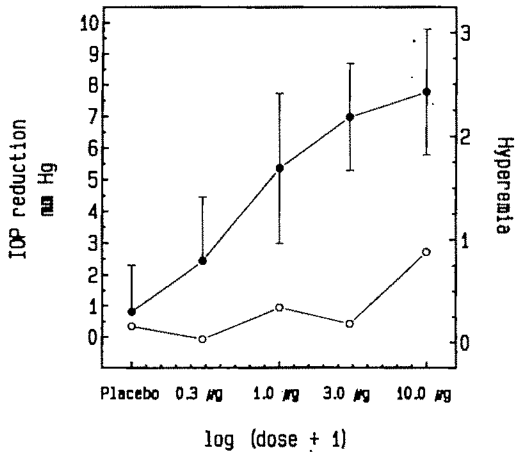

Figure 1 The effect on IOP and conjunctival hyperaemia of four single doses of PhXA34 and placebo. The values used to express the IOP reduction for each dose are based on the IOP determinations at t_8 and t_{12}. These two values were averaged and the difference between average IOP day 1 (before treatment) and average IOP day 2 (after treatment) was used as an estimate of drug effect for each patient. Hyperaemia was estimated for each patient as the difference between maximum score on day 2 (after treatment) and the registration at t_0 day 2. Closed circles: mean IOP reduction with 95% confidence interval; open circles: mean hyperaemia.

Table 1 Forty patients were randomised to one of five different treatments with eight patients in each group. The baseline characteristics for the different treatment groups are shown

	Placebo	*0·3 µg*	*1 µg*	*3 µg*	*10 µg*
Number	8	8	8	8	8
Females	8	5	6	6	7
Males	0	3	2	2	1
Mean age	58·9	64·4	67·6	58·4	65·0
STD	10·4	6·6	5·6	12·2	8·0
Range	45–73	56–75	56–78	41–72	54–75
IOP	22·4	22·8	23·2	22·8	23·1
STD	2·54	3·83	4·40	2·47	2·95
Exfoliations	3	4	6	0	3
Right eyes	3	6	4	3	2
Left eyes	5	2	4	5	6

IOP is expressed as the mean of pretreatment day t_0, t_8, and t_{12}.

The contralateral eyes were a mixed group of normal eyes and eyes with ocular hypertension, and they have not been included in the analysis.

The estimated hyperaemia is based on the difference between the maximum score on day 2 and the score before examination and IOP measurement at t_0 day 2.

Results

All patients completed the study. The results of randomisation are shown in Table 1. Figure 1 shows the average IOP reductions (mean with 95% confidence interval) for placebo and increasing doses of PhXA34 8 and 12 hours post-dose.

Table 2 IOP in the study eyes for the different treatment groups day 1 and day 2

Time	*Day 1*	*Day 2*	*Change in IOP*
Placebo			
0	24·9 (23·2–26·6)	25·8 (22·5–29·0)	−0·9 (2·0– −3·8)
0·5		26·8 (24·0–29·5)	−1·0 (−0·1– −1·9)
8	20·8 (19·2–22·3)	20·1 (18·5–21·8)	0·6 (1·6– −0·4)
12	21·6 (20·2–23·0)	20·6 (17·9–23·4)	1·0 (2·9– −0·9)
24	25·8 (22·5–29·0)	22·9 (20·2–25·5)	2·9 (5·4– −0·4)
PhXA34 0·3 µg			
0	24·9 (22·1–27·6)	23·9 (20·1–27·7)	1·0 (3·4– −1·4)
0·5		25·1 (21·8–28·5)	−1·3 (1·2– −3·7)
8	20·6 (17·7–23·5)	18·9 (16·9–20·8)	1·8 (3·7– −0·0)
12	23·0 (19·8–26·2)	19·9 (16·0–23·8)	3·1 (5·1– 1·2)
24	23·9 (20·1–27·7)	21·9 (19·3–24·5)	2·0 (4·7– −0·7)
PhXA34 1 µg			
0	25·8 (20·5–31·0)	24·5 (21·1–27·9)	1·3 (4·3– −1·8)
0·5		23·4 (18·4–28·4)	1·1 (3·2– −1·0)
8	22·0 (20·5–23·5)	17·1 (14·8–19·4)	4·9 (6·5–3·2)
12	21·9 (19·3–24·4)	16·4 (13·1–19·7)	5·5 (8·6–2·4)
24	24·5 (21·1–27·9)	21·5 (17·4–25·6)	3·0 (5·5–0·5)
PhXA34 3 µg			
0	24·5 (22·1–26·9)	23·5 (20·8–26·2)	1·0 (3·2– −1·2)
0·5		24·0 (22·1–25·9)	−0·5 (2·1– −3·1)
8	21·8 (20·6–22·9)	15·0 (13·0–17·0)	6·8 (8·4–5·1)
12	22·0 (20·2–23·8)	14·4 (11·8–16·9)	7·6 (9·4–5·8)
24	23·5 (20·8–26·2)	20·3 (17·7–22·8)	3·3 (5·2–1·3)
PhXA34 10 µg			
0	24·4 (21·2–27·6)	24·0 (20·8–27·2)	0·4 (2·5– −1·8)
0·5		24·9 (21·4–28·4)	−0·9 (1·0– −2·8)
8	22·5 (21·0–24·0)	15·5 (14·2–16·8)	7·0 (8·1–5·9)
12	22·4 (20·1–24·7)	14·5 (13·7–15·3)	7·9 (10·5–5·2)
24	24·0 (20·8–27·2)	18·6 (17·2–20·0)	5·4 (8·1–2·7)

The values are means in mm Hg with 95% confidence interval. The drug was given topically shortly after t_0 (7 am) on day 2. The change in IOP is calculated as IOP day 1 minus IOP day 2 at the corresponding time of the day except for the $t_{0\text{-}5}$ value which is compared with the IOP just before drug application (t_0 on day 2). IOP values t_{24} on day 1 are identical to the values t_0 on day 2, but listed to make comparison easier. Negative values indicate an increase in IOP and positive values indicate a reduction in IOP. There were eight patients in each group.

Table 3 The degree of hyperaemia in the study eyes. The procedures used for the grading are described in the text

Treatment time	*Grade of hyperaemia* 0	0·5	1	1·5	2	2·5	3
Placebo							
* 0	0	5	2	0			
* 8	2	4	1	0			
* 12	1	3	3	0			
* 24	3	1	1	2			
PhXA34 0·3 µg							
0	1	3	4	0			
* 8	3	3	1	0			
12	2	3	3	0			
24	4	2	1	1			
PhXH34 1·0 µg							
* 0	0	5	2	0			
* 8	0	3	4	0			
* 12	0	3	2	2			
* 24	1	2	3	1			
PhXA34 3·0 µg							
* 0	1	3	3	0			
* 8	0	2	3	1			
* 12	1	2	3	1			
* 24	2	5	0	0			
PhXA34 10·0 µg							
0	0	4	4	0	0		
8	0	0	3	4	1		
12	0	0	2	4	2		
24	0	0	5	2	1		

The numbers in each column indicate the number of eyes with the specific grade of hyperaemia.
The drug was given shortly after t_0.
*Notifies that the number of photographs in that row is 7.

They were 0·8 (−0·7–2·3), 2·4 (0·4–4·5), 5·4 (3·0–7·8), 7·0 (5·3–8·7) and 7·8 (5·8–9·8) mm Hg. The corresponding reductions expressed as a percentage of IOP on day 1 were 4%, 11%, 25%, 32% and 35%.

When compared with placebo 1, 3, and 10 µg PhXA34 were significantly better in reducing the IOP whereas 0·3 µg was not significantly changed from placebo: 0·3 µg $p<0·1$, 1 µg $p<0·002$, 3 µg $p<0·001$, 10 µg $p<0·001$; (*t* test for two independent means with pooled estimate of common variance).

Table 2 presents the IOP values on day 1 and day 2 for the five different treatment groups including the differences in IOP between the 2 days.

The change in IOP for the different treatment groups can also be expressed as area under the curve and these values were for placebo and increasing doses of PhXA34: 24 (−15–65), 42 (−12–96), 94 (38–153), 118 (72–164), 132 (82–184). Values are means in mm Hg hours with upper and lower limits for the 95% confidence interval.

IOP was measured 30 minutes after the drug application on day 2 and at that time no significant effect on IOP was found for any dose of PhXA34.

No discomfort was felt by any patient before drug application, but mild discomfort was noted by a total of seven patients at some time during the remaining part of day 2. Symptoms in both eyes with no difference between the two eyes were felt by three patients. Discomfort in the treated eye only, mainly in the form of a mild foreign body sensation, was reported by four patients: one placebo treated, two treated with 1 µg PhXA34, and one treated with 3 µg PhXA34. Additionally, headache was reported by one patient treated with placebo.

No significant difference in hyperaemia between study eyes and contralateral eyes was present in any treatment group before drug application. No hyperaemia was observed for any dose 30 minutes after drug application, and hyperaemia was practically absent for doses lower than 10 µg. This dose however produced observable hyperaemia grade 1·5–2 in most patients (Table 3). Photographs were not achieved from three patients due to camera problems. These patients were treated with placebo, 1 µg, and 3 µg PhXA34 respectively, and the 8-hour photograph from a patient treated with 0·3 µg PhXA34 was not possible to grade. No flare or cells were seen in the anterior chamber.

Discussion

The result of randomisation did not show any important differences except for an uneven distribution of the 16 eyes with exfoliations. The high frequency of patients with exfoliations reflects the expected distribution in a group of patients with ocular hypertension in the northern part of Sweden.

A prior study has shown a clear dose-related IOP reduction in normal eyes.[6] A dose-related response was also found in this study with regard to IOP reduction; 3 and 10 µg PhXA34 seem to be almost equipotent with regard to IOP reduction based on average IOP reduction 8 and 12 hours post dose, but 10 µg appears more potent if the IOP reduction 24 hours after the dose is included as in the values expressed as area under the curve. The 8 and 12 hours average IOP reduction was chosen as the primary variable for this dose-response study because it is known from prior studies that the maximal effect is observed within this period for most doses. In this study the maximal effect is seen 12 hours after the dose for all doses of PhXA34, and the inclusion of the 8-hour values therefore results in a slight underestimate of the peak IOP reduction.

In the contralateral eyes we observed only minor fluctuations in IOP with a tendency towards a slight IOP reduction of normally less than 1 mm Hg on day 2, and these changes seemed to be completely unrelated to the dose given in the study eye. Hyperaemia was negligible for doses lower than 10 µg PhXA34 suggesting that the dose-response curve for hyperaemia is displaced to the right of the IOP dose-response curve. This is in contrast to the hyperaemia observed after $PGF_{2\alpha}$-IE where all effective doses caused some hyperaemia. There is also a difference in the timing of the hyperaemia since none was visible for any dose of PhXA34 30 minutes after application, while $PGF_{2\alpha}$-IE produces maximal hyperaemia within the first hour. High doses of $PGF_{2\alpha}$-IE also caused an initial increase in IOP, probably due to intraocular vasodilation, something that was not observed even with 10 µg PhXA34.

In summary PhXA34 is a potent ocular hypotensive agent also in patients with ocular hypertension, where one topical dose of 3 µg reduce IOP about 32% 8–12 hours after application without clinically significant side effects.

PhXA34 eye drops and project support were supplied by Kabi Pharmacia Ophthalmics AB, Uppsala, Sweden. The authors have no commercial or proprietary interest in PhXA34 eye drops.

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FIFTY YEARS AGO

Paper Salvage

Our readers will probably have noticed the slight difference in texture and tint of the paper used for printing the Journal since the beginning of this year. Our stock of paper came to an end in December last and like everybody else we have had to make do with what the controller allows us. In after years it may be of interest as dating some of the War years. Deterioration in quality of paper during war is no new thing. Exactly the same happened in the Napoleonic struggle. Much of the paper used in the earlier years of the last century was very poor in quality and no one now-a-days would dream of reading such a thing as the first edition of Waverley (published 1814), if he could get a later edition.

It behoves us all to contribute as much as we can to the paper salvage campaign. For ourselves we almost tremble to think of the numbers of galleys of back numbers which we have sent to the pulping machine. Old books, old letters, old receipts and paper of every kind are badly needed. It has been rather a wrench to cast out copies of old text-books which we used in the days of our studentship. Some of these were at least forty years out of date but had a sentimental interest to us.

Those who were brought up in Victorian days will be aware of the hoarding propensities of parents in the matter of family and other letters. A great many, but not all, of these are very suitable for salvage. Young hopeful's reiterated appeals from school for a hamper or a new cricket bat or even a modest half-a-crown are not worth keeping, but no one in his senses would destroy letters by eminent hands. If, in going through bundles of old correspondence, one lights upon a letter, for instance, from the poet Wordsworth to one's own grandfather it will be wise to preserve it, for its value may appreciate in post-war times.

Br J Ophthalmol 1942; **26**: 225–6.

British Journal of Ophthalmology, 1992, 76, 218–220

Twin study on cup/disc ratio of the optic nerve head

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Abstract

Seventeen healthy twin pairs (10 monozygotic and seven dizygotic) from the Finnish Twin Cohort Study were examined to study the impact of heredity *v* environment in the determination of cup-to-disc area ratio. These twins were free from any known eye disease. The cup/disc ratio was determined using stereo photography and a computer assisted analysis technique. The zygosity of all twin pairs was confirmed with the DNA 'fingerprint' technique. The intrapair correlations were high among monozygotic pairs compared with those among dizygotic twin pairs. The difference of cup/disc area ratios between the right eyes of members of monozygotic twin pairs was statistically significantly smaller than that of dizygotic twin pairs ($p<0\cdot001$). The same was true for left eyes ($p<0\cdot01$). This result confirms a genetic determination in cup/disc area ratio in normal eyes.

A previous study of Armaly has shown that the cup/disc ratio of the optic nerve head is genetically determined.[1] He examined parent-offspring and sibling-sibling pairs and found that the cup/disc ratios of these first degree relatives were similar. He found no such similarity between husband-wife pairs. The problem with such a genealogical model is that both genetic and environmental factors could cause sib-sib and parent-offspring similarities. It seems obvious that the effects of genes and environment need to be separated to confirm this important finding. One way to separate these two sources of variation is the twin study method. Here the simultaneous occurrence of a disease or trait in both members of a twin pair is called concordance. When the disease affects only one member of a pair it is called discordance. The twin method compares the concordances among monozygotic twins with that of dizygotic twins. In a monogenetically transmitted disease the monozygotic twins should be 100% concordant and the dizygotic twins 50% concordant. When a continuous trait is under study the within-pair correlations among monozygotic twin pairs are compared with those among dizygotic pairs. The excess correlation among monozygotic pairs is attributed to genetic effects to the trait. We used the nationwide Finnish Twin Cohort Study to apply the twin method to cup/disc ratio of the optic nerve head.

Material and methods

The pairs were selected randomly from one age stratum (34–35 years) of a nationwide twin registry called the Finnish Twin Cohort Study (FTCS). The compilation, zygosity determination, and description of the cohort have been presented in previous publications.[2-6] This twin cohort comprises all twin pairs in Finland and currently includes 16 000 twin pairs both monozygotic and same-sexed dizygotic. Twenty pairs were invited to the study (compliance 90%). A complete clinical eye examination was performed including visual acuity, objective refraction, slit-lamp examination, applanation tonometry, indirect ophthalmoscopy, and ultrasound measurement of the axial length and anterior chamber depth. The optic nerve head was photographed with a Canon fundus camera on black and white film. The stereo base was created using lateral shifting technique. Optic disc, cup, and neuroretinal rim areas as well as cup/disc area ratios were digitised manually from the stereophotographs with a computer assisted technique. The software incorporates algorithms to take into account image magnification/minification induced by axial ametropias.[7] As a result actual optic disc and optic cup areas were obtained in square millimetres. The examiner of the stereo photographs was unaware of the identity of the particular eye under study. The zygosity has been determined for the whole cohort by a questionnaire method.[6] It was verified in this particular sample by the DNA 'fingerprint' technique.[8] Figure 1 shows an example of one monozygotic and one dizygotic pair and their DNA 'fingerprints'. The bands for a mono-

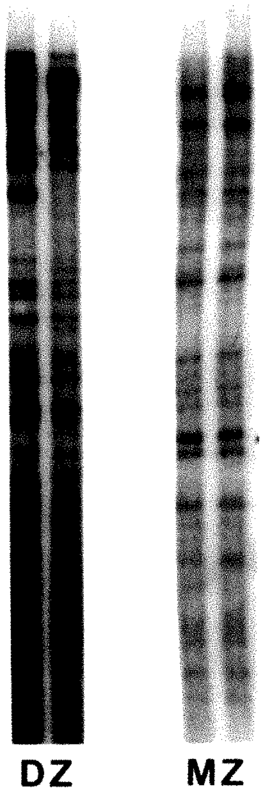

Figure 1 DNA 'fingerprints' of a monozygotic (MZ) and dizygotic (DZ) twin pair showing the exact similarity of bands in the monozygotic pair.

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Accepted for publication
22 August 1991

Table 1 Mean disc areas, cup areas, and cup/disc ratios by zygosity and laterality (value of member A/value of member B)

	Disc area	*SD*	*Cup area*	*SD*	*Rim area*	*SD*	*Cup/disc ratio*	*SD*
MZ								
Right eyes	2·23/2·13	0·39/0·47	0·71/0·59	0·40/0·43	1·52/1·54	0·20/0·32	0·30/0·26	0·13/0·15
Left eyes	2·14/2·14	0·37/0·34	0·61/0·55	0·39/0·40	1·52/1·59	0·36/0·29	0·28/0·25	0·16/0·14
DZ								
Right eyes	2·19/2·11	0·46/0·31	0·38/0·43	0·39/0·28	1·80/1·68	0·23/0·24	0·16/0·19	0·14/0·12
Left eyes	2·03/2·06	0·38/0·32	0·37/0·40	0·26/0·34	1·66/1·65	0·29/0·18	0·18/0·18	0·10/0·13

zygotic twin pair are exactly alike while the dizygotic pairs differ in several bands.

One pair from the original 20 pairs invited was discarded because the second member of the pair was unable to attend the examination because of estimated delivery in 2 weeks. Another pair was discarded from this analysis because of missing photographs of the second member of the pair. One pair was discarded because one member of the pair did not attend the clinical examination. One eye of a dizygotic twin was discarded from the calculations because of a non-alternating strabismus and amblyopia. All eyes in the calculations had normal visual acuity and no previous or present eye disease.

Results

The mean disc areas, cup areas, and cup/disc ratios for both zygosity classes and zygosities are given in Table 1. In Figure 2 the distributions of the cup/disc ratios are given. From the figure it appears that the cup/disc ratios are not normally distributed. Because of this a non-parametric statistic was chosen in the calculations of correlation (Spearman rank correlation). The correlations in cup/disc ratios between right and left eyes in the same individual showed high correlations in both MZ and DZ twin pairs (Table 2). The correlations between right-right and left-left eyes between two members of a monozygotic twin pair were fourfold compared with the same correlations among two members of a dizygotic twin pair (Table 3). The mean absolute differences in cup/disc area ratio between right (0·062) and left (0·037) eyes of monozygotic twins were statistically significantly lower than right (0·181) and left (0·132) eyes of dizygotic twins ($p<0{\cdot}001$ right eyes, $p<0{\cdot}005$ left eyes, Wilcoxon two-sample test). In Figure 3 an example of an optic nerve head of a monozygotic and a dizygotic pair (right eyes of twin sisters) is shown. The cup/disc ratios are remarkably similar between the two members of the monozygotic pair while there is a substantial difference in the dizygotic twin pair (right eyes of twin sisters).

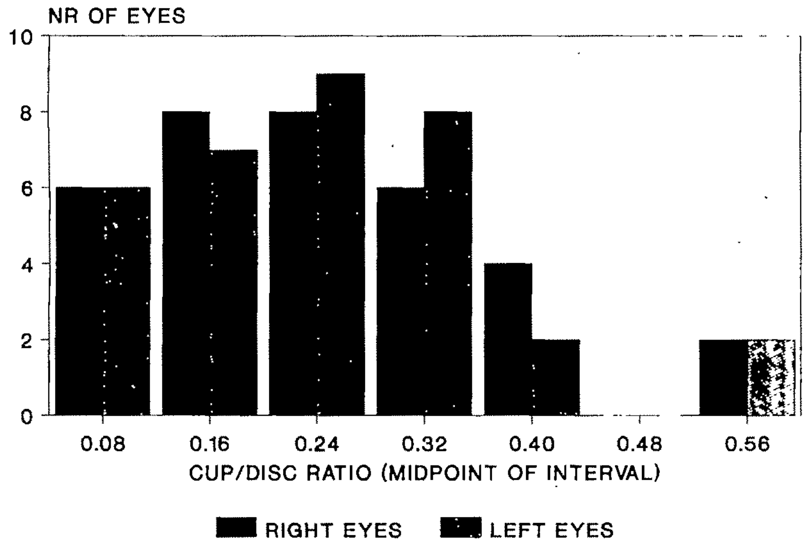


Figure 2 Distribution of cup/disc area ratios in this sample of 17 twin pairs.

The result of this study supports the theory of a strong genetic determination of cup/disc ratio in normal eyes.

Discussion

The present material confirms the genetic nature of determination of the cup/disc area ratio in a normal eye.

The disc areas were similar in both monozygotic and dizygotic pairs but the cup areas were smaller among dizygotic twin pairs both in right and left eyes. The smaller mean cup sizes and cup/disc ratios in dizygotic twin pairs could decrease the differences among dizygotic twin pairs thus resulting in an underestimation of heredity in this sample and hereby increasing the validity of our conclusion.

Table 2 Intra-individual correlations in cup/disc ratios between right and left eyes of 10 MZ and seven DZ twin pairs (Spearman rank correlation)

MZ		
	A ODX	B ODX
A OSIN	0·90	
B OSIN		0·82
DZ		
	A ODX	B ODX
A OSIN	0·64	
B OSIN		0·80

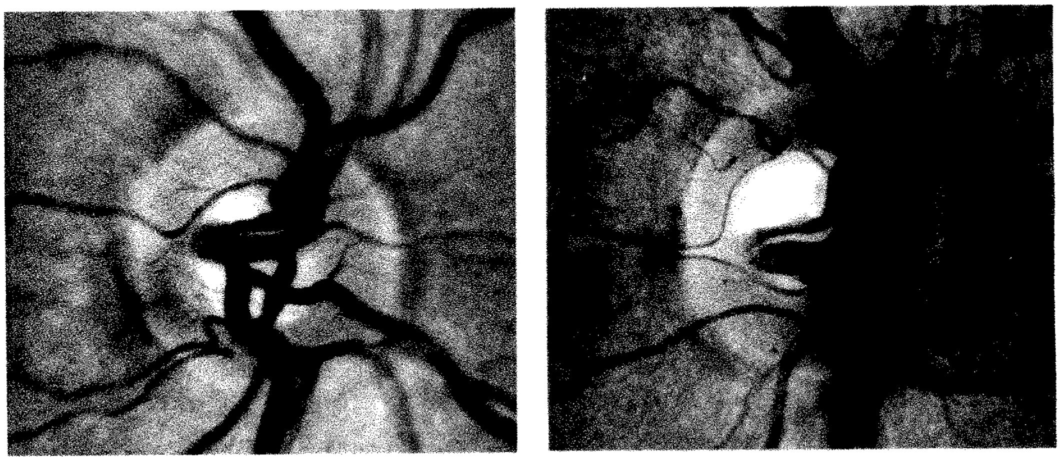
A=first member of a twin pair.
B=second member of a twin pair.
ODX=right eye.
OSIN=left eye.

Table 3 Intrapair correlations of cup/disc ratios of 10 monozygotic and seven dizygotic twin pairs (Spearman rank correlation). (The correlations are shown separately for right eyes and left eyes of twin pairs)

MZ		
	A ODX	A OSIN
B ODX	0·88	
B OSIN		0·98
DZ		
	A ODX	A OSIN
B ODX	0·19	
B OSIN		0·14

A=first member of a twin pair.
B=second member of a twin pair.
ODX=right eye.
OSIN=left eye.

Monozygotic pair



Dizygotic pair

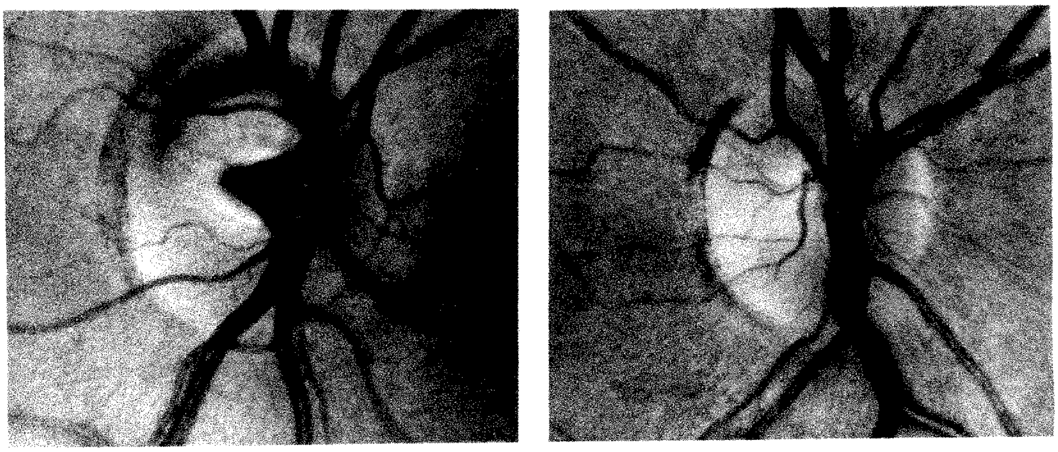


Figure 3 Example of the optic nerve head of a monozygotic and a dizygotic twin pair. The upper two pictures represent right eyes of a female monozygotic pair showing a significant similarity of the cup/disc ratio. The lower two pictures represent right eyes of a female dizygotic pair showing a significant dissimilarity in the cup/disc ratio.

The distribution of cup/disc area ratios in this sample was skewed. Lower values were over-represented. This is in accordance with previous findings by Armaly.[1] The high correlation between two eyes of any given individual was confirmed in the present sample. A previous study by Armaly showed that the cup/disc ratio differed less than 0·1 in 92% of 1098 subjects and less than 0·2 in 99% of subjects. In large samples of healthy individuals the cup/disc ratio of one eye alone or mean of both eyes can be used without causing bias due to intraperson variation between the two eyes.

The high heritability of the cup/disc ratio in normal eyes has important implications. It has been shown previously by Armaly that the cup/disc ratio of first degree relatives of glaucoma patients does not show a different distribution from that in the general population.[1] This might imply that while the cupping of the optic nerve head itself is genetic in origin that of glaucomatous cupping is affected by environmental factors or perhaps a gene-environment interaction.

The liability to glaucoma might still be controlled genetically in part. The heritability of determination of the cup/disc ratio in a healthy eye would bias the heritability estimates of glaucoma if the cup/disc ratio is used as a major criterion for diagnosis.

This study was supported by grants from Silma ja Kudospankkisaatio, Silmasaatio, and Suomen Kulttuurirahasto. From the Kimura Laboratory of Clinical Investigation, Beckman Vision Center.

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British Journal of Ophthalmology, 1992, 76, 221–224

Cystoid macular oedema following cataract extraction in patients with diabetes

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Accepted for publication 29 August 1991

Abstract

The course of cystoid macular oedema (CMO) following extracapsular cataract extraction with posterior chamber intraocular lens implantation was prospectively studied in 44 eyes of 44 consecutive diabetic patients without preoperative CMO. In 50% of eyes CMO was observed 6 weeks after surgery and in 25% was still present at 1 year. The preoperative presence of diabetic retinopathy significantly affected the postoperative onset and persistence of CMO. CMO occurred postoperatively in only 32% of eyes without pre-existing diabetic retinopathy and in 81% of eyes with pre-existing diabetic retinopathy ($p<0.05$). CMO persisted at 1 year after surgery in only 7% of eyes without pre-existing diabetic retinopathy and in 56% of eyes in which diabetic retinopathy persisted ($p<0.01$). Angiographic CMO (that is, detectable only on fluorescein angiography) was more common than clinical CMO (detectable on ophthalmoscopic examination as well) in eyes with no pre-existing diabetic retinopathy, whereas clinical CMO was seen more often than angiographic CMO when diabetic retinopathy was present preoperatively ($p<0.01$). The course and final visual outcome of angiographic CMO were more favourable than in clinical CMO. Final visual acuity of at least 6/12 was achieved in 86% of eyes with angiographic CMO and in only 33% of eyes with clinical CMO. On the basis of the above findings we believe that cataract extraction should not be recommended for eyes with pre-existing diabetic retinopathy until the vision has deteriorated to at least 6/30–6/60.

The visual prognosis following cataract surgery in diabetic patients depends on the presence and/or the severity of existing diabetic retinopathy and its possible aggravation after surgery.[1-6] In particular the visual outcome may be influenced by the postoperative onset of cystoid macular oedema (CMO) which may occur even without onset or aggravation of diabetic retinopathy.

In a previous study we observed a high incidence of progression of diabetic retinopathy following cataract surgery.[7] 'Progression' was defined as appearance or worsening of the diabetic retinopathy regardless of whether or not CMO was present. However though that study did not deal specifically with the course of maculopathy our clinical impression was that the presence of CMO after cataract extraction is more common in diabetic than in non-diabetic eyes.

The purpose of this prospective study was to investigate the onset and course of CMO following cataract surgery with lens implantation in diabetic patients. The diabetic patients in this study all underwent extracapsular cataract extraction with posterior chamber lens implantation and did not have CMO prior to surgery.

Subjects and methods

Included in this study were 44 eyes of 44 consecutively diabetic patients, with or without diabetic retinopathy who underwent extracapsular cataract extraction with posterior chamber intraocular lens implantation in our department between January 1987 and January 1990 and who met the following criteria: (1) diagnosis of diabetes mellitus at least 6 months prior to cataract surgery; (2) uneventful surgical procedure, performed by a team of senior specialists in cataract surgery; (3) no evidence of CMO prior to surgery or, where the cataract had precluded visualisation of the fundus preoperatively, within the first 3 days after surgery; (4) no laser treatment for diabetic retinopathy given or required before or within 1 month after surgery. This restricts the series to eyes in which diabetic retinopathy if present at the time of surgery, was of the mild non-proliferative type; (5) no other ocular disorders; (6) postoperative follow-up for at least 1 year; (7) a fundal examination prior to and/or within 3 days after surgery as a baseline for postoperative assessment of retinal status; (8) additional fundal examinations during three distinct periods within the first year of postoperative follow-up: (a) from the second week to the end of the third month; (b) from the fourth to the end of the sixth month; and (c) from the seventh to the end of twelfth month.

All patients underwent routine fluorescein angiography 6 weeks and 6 months after surgery. In those cases where onset or progression of diabetic retinopathy had occurred and/or fluorescein angiography revealed persistence of CMO after 6 months additional angiograms were obtained every 2 months until the end of the study, which was 1 year after surgery. In cases where CMO was not demonstrated initially on the angiogram but was suspected on the basis of an ophthalmoscopic examination angiography was repeated. Fundal examinations, colour fundal photography, and fluorescein angiography readings were performed by a retinal specialist.

After surgery if the severity of diabetic retinopathy and/or macular oedema met the criteria for treatment as outlined by the Diabetic Retinopathy and Early Treatment Diabetic Retinopathy Studies argon laser photocoagulation was performed in accordance with their recommendations.[8 9] Laser treatment consisted of panretinal photocoagulation for proliferative or very

Table 1 Clinical features of diabetic and non-diabetic patients with and without CMO and control patients following cataract surgery

	Diabetic patients (n=44)		*Non-diabetic patients (n=25)*	
	No CMO (n=22 eyes)	*CMO (n=22 eyes)*	*No CMO (n=23 eyes)*	*CMO (n=2 eyes)*
Age (years), mean (SD)	65·6 (8)	67·9 (7)	72·6 (7)	65
range	52–78	42–82	50–88	64–66
Duration of DM* (years), mean (SD)	9·5 (9)	15·8 (6)	–	–
range	½–23	2–26		
	No of patients (%)			
Male:female	6:16 (27:73)	8:14 (36:64)	9:14 (39:61)	1:1 (50:50)
Management of DM:			–	–
Diet	5 (23)	–		
Oral agents	14 (64)	14 (64)		
Insulin/insulin and oral	3 (14)	8 (36)		
Vascular disease:				
Hypertension	8 (36)	11 (50)	7 (30)	–
Cardiac	5 (23)	3 (14)	2 (9)	–

*Diabetes mellitus.

severe non-proliferative diabetic retinopathy, and/or focal or grid argon green laser photocoagulation for macular oedema.[8, 9]

For each patient a standardised medical protocol was completed giving detailed demographic and clinical information including duration of diabetes mellitus, presence of other systemic diseases, and medications. The ocular findings recorded during each follow-up period included best corrected visual acuity, applanation tonometry, biomicroscopy, Goldman three-mirror examination, and indirect ophthalmoscopy; also recorded were the findings of pre- and postoperative fluorescein angiography and the results of laser treatment.

Cystoid macular oedema was diagnosed as angiographic if fluorescein angiography revealed the typical appearance of CMO as described by Gass and Norton,[10] and as clinical if CMO was demonstrated on both fluorescein angiography and fundal examination.

On the basis of the macular findings eyes were divided into three groups: eyes that did not develop CMO, eyes with angiographic CMO only, and eyes with clinical CMO. On the basis of the diabetic retinal findings two subgroups were identified. The first, defined as the 'no change' subgroup consisted of eyes in which the retinal status remained unchanged following surgery regardless of whether or not diabetic retinopathy was present preoperatively. The second, termed the 'progression' subgroup, consisted of eyes in which diabetic retinopathy first appeared or progressed following surgery. Progression was considered to have occurred when: (1) a patient with no pre-existing diabetic retinopathy developed either non-proliferative diabetic retinopathy or proliferative diabetic retinopathy after surgery; or (2) a patient with pre-existing non-proliferative diabetic retinopathy showed postoperative aggravation of the non-proliferative changes or development of proliferative diabetic retinopathy as previously described by us.[5]

Table 2 Postoperative development of clinical and angiographic CMO in relation to the preoperative status of diabetic retinopathy

	Postoperative development of CMO (n=44 eyes)		
	Angiographic CMO‡ 7 (16%)	*Clinical CMO§ 15 (34%)*	*Total 22 (50%)*
Preoperative status:	*No of eyes/total (%)*		
No DR* (n=28 eyes)	6/28 (21)	3/28 (11)	9/28 (32)
DR† (n=16)	1/16 (6)	12/16 (75)	13/16 (81)
	$p<0·01$		

*No diabetic retinopathy; †Diabetic retinopathy; ‡Angiographic CMO only; §Ophthalmoscopic and angiographic CMO.

The control group consisted of 25 eyes of 25 consecutive non-diabetic patients who underwent the identical surgical procedure performed by the same surgical team during the same period and who met our inclusion criteria nos. 2 and 5–8 listed above.

The χ^2 test was used for statistical analysis.

Results

Of the 44 patients in the study group 14 were men and 30 were women. The mean age at the time of surgery was 66·7 years (range 42 to 82) and the mean duration of diabetes mellitus was 12·6 years (range 6 months to 26 years). Cataract extraction was unilateral in 36 patients and bilateral in eight. In the bilateral cases only one eye, the one operated on first, was included in the study. Of the 25 patients in the control group 10 were men and 15 were women. Their mean age at the time of surgery was 71·2 years (range 50 to 88) (Table 1).

Following surgery 22 eyes in the study group (50%) developed CMO compared with two eyes (8%) in the control. Table 1 compares the clinical features of patients with and without postoperative onset of CMO. Differences between patients in this respect were not significant though patients with CMO had diabetes mellitus of longer duration than those without CMO, and more patients in the group with CMO needed insulin.

Clinical CMO was diagnosed in 15 eyes in the study group (34%) and angiographic CMO only in seven (16%). The corresponding findings in the control group were one eye (4%) in each category; the angiographic CMO subsequently disappeared but the clinical CMO persisted. The relationship between the preoperative diabetic retinal status and the onset of clinical or of angiographic CMO in the 22 study group eyes that developed CMO is summarised in Table 2. The relationship between the preoperative diabetic retinal status and the postoperative course of diabetic retinopathy and of CMO is presented in Table 3. Table 4 summarises the incidence of CMO and its persistence 1 year after surgery in relation to both the preoperative and the postoperative status of diabetic retinopathy.

Of the 13 eyes with preoperative diabetic retinopathy and postoperative onset of CMO, nine also showed progression of diabetic retinopathy following surgery. Five of these 13 eyes received laser treatment for their postoperative retinopathic changes and eight did not. In the nine eyes that had no diabetic retinopathy preoperatively and developed CMO postoperatively laser treatment was not indicated (Table 4).

Table 5 compares the final visual acuity results in diabetic patients with and without postoperative onset of CMO. In both cases more patients

Table 3 Postoperative course of diabetic retinopathy and onset of CMO in relation to the preoperative status of diabetic retinopathy

	Postoperative status of diabetic retinopathy (n=44 eyes) No of eyes (%)			
	No change of DR 26 (59)		*Progression of DR 18 (41)*	
Preoperative status	*Without CMO 18 (69)*	*With CMO 8 (31)*	*Without CMO 4 (22)*	*With CMO 14 (78)*
No DR* (n=28 eyes)	17/28 (61)	4/28 (14)	2/28 (7)	5/28 (18)
DR† (n=16 eyes)	1/16 (6)	4/16 (25)	2/16 (13)	9/16 (56)
	p<0·025		NS	

*No diabetic retinopathy.
†Diabetic retinopathy.
NS, not significant.

achieved a final vision of at least 6/12 if there was no diabetic retinopathy prior to surgery. As shown in Table 6 the visual acuity results were better in patients with angiographic than with clinical CMO. In our control group the visual acuity results of eyes that did not develop CMO were similar to those of the diabetic patients with non-pre-existing diabetic retinopathy and no CMO. The eye with persistent CMO had a final visual acuity of 6/30.

Discussion

None of the diabetic patients in this series had CMO prior to cataract surgery but 50% (22 eyes) developed it postoperatively. The occurrence of CMO after surgery in these eyes could have been a consequence of the operation itself (pseudophakic CMO) or of postoperative deterioration of diabetic retinopathy (diabetic CMO), or both. Since it was not possible to distinguish between them all cases of CMO were included in our analysis of the results.

Our definition of CMO as 'angiographic' in this study was based on typical findings on fluorescein angiography as described by Gass and Norton.[10] After cataract surgery a diagnosis of clinical CMO is usually based not only on typical angiographic findings but also on poor visual acuity (<6/12)[11]; however, we considered visual acuity to be an unreliable criterion here as our cases included eyes with diabetic retinopathy, itself a possible factor affecting visual acuity. We therefore diagnosed CMO as 'clinical' on the basis of ophthalmoscopic (in addition to angiographic) findings.

In non-diabetic eyes angiographic CMO following extracapsular cataract extraction with posterior chamber lens implantation reportedly occurs in as many as 44% of cases.[11 12] In our control group it occurred in only 8% (2/25) compared with an incidence of 50% in the diabetic eyes. It should be noted however that the occurrence of CMO in the diabetic eyes appeared to be influenced by the pre- or postoperative diabetic retinal status and especially by the former: it occurred in 81% (13/16) of eyes that had pre-existing diabetic retinopathy and in only 32% (9/28) of eyes that did not. Since pre-existing diabetic retinopathy is also a risk factor for its postoperative aggravation,[7] which may be associated with CMO, it is possible that the pre-existence of diabetic retinopathy may have contributed to the postoperative development of CMO. In this study most of the eyes with postoperative progression of diabetic retinopathy also developed CMO (78%, 14/18), whether diabetic retinopathy had pre-existed (82%, 9/11) or not (71%, 5/7) (Table 3).

In the general population CMO, if it appears at all after surgery, usually occurs within 6 weeks of the operation, is transitory, and disappears within 6 months.[11] The reported incidence of CMO persisting for 6 months after surgery ranges between 0·9 and 4%.[11 13-15] In our control group it persisted in 4%. In the diabetic group however CMO lasted longer and was still evident even after 6 months. We therefore considered CMO as 'persistent' if it was still present at 1 year after surgery (Table 4). Persistence of CMO was noted in 25% of the diabetic eyes and like the postoperative incidence of CMO in these eyes varied with the preoperative retinal status (see Table 4). If we assume that persistence of CMO for at least 1 year after surgery in diabetic patients is equivalent to its persistence for at least 6 months in the general population then our diabetic patients with no pre-existing diabetic retinopathy did not differ significantly from our control group in this regard (7% *v* 4% respectively). Eyes with pre-existing diabetic retinopathy that progressed after surgery (89%, 8/9) carried the highest risk of persistence.

Visual acuity of at least 6/12 was achieved by a high percentage of eyes that developed angiographic CMO after surgery, similar to the percentage in the subgroup of operated patients with no pre-existing diabetic retinopathy and no CMO (Table 5, 6). Similar findings have been reported by others.[12] In eyes that developed clinical CMO the visual acuity outcome was less favourable, especially in the subgroup with pre-

Table 4 Postoperative course of CMO in relation to pre- and postoperative status of diabetic retinopathy

	Postoperative course of CMO (n=22 eyes) No of eyes/total (%)								
	CMO with no change of DR			*CMO with progression of DR*			*Total*		
Preoperative status	*Appearance (n=8)*	*Persistence after 6 months (n=8)*	*Persistence after 1 year (n=2)*	*Appearance (n=14)*	*Persistence after 6 months (n=12)*	*Persistence after 1 year (n=9)*	*Appearance (n=22)*	*Persistence after 6 months (n=20)*	*Persistence after 1 year (n=11)*
No DR*	(n=21) 4/21	4/21	1/21	(n=7) 5/7	3/7	1/7	(n=28) 9/28 (32)	7/28 (25)	2/28 (7)
DR†	(n=5) 4/5‡	4/5	1/5	(n=11) 9/11§	9/11	8/11	(n=16) 13/16 (81)	13/16 (81)	9/16 (56)
							Total: 22/44	20/44 (45)	11/44 (25)
							p<0·05		p<0·01

*No diabetic retinopathy; †Diabetic retinopathy; ‡Argon laser treatment was applied in two cases: in one the CMO resolved and in the other it persisted; §Argon laser treatment was applied in three cases: in all of them CMO persisted.

Table 5 Comparison of visual acuity results in diabetic eyes with and without CMO after cataract surgery in relation to preoperative status of diabetic retinopathy

	Without CMO (n=22 eyes)			*With CMO (n=22 eyes)*		
	No DR (n=19)*	*DR† (n=3)*	*Total (n=22)*	*No DR (n=9)*	*DR (n=13)*	*Total (n=22)*
Visual acuity	*No (%)*					
>6/12	16 (84)	–	16 (73)	6 (67)	5 (38)	11 (50)
6/15–6/30	3 (16)	2 (67)	5 (23)	3 (33)	8 (62)	11 (50)
<6/30	–	1 (33)	1 (4)	–	–	–

*No diabetic retinopathy.
† Diabetic retinopathy.

Table 6 Visual acuity results in diabetic eyes with clinical and angiographic CMO following cataract surgery in relation to preoperative status of diabetic retinopathy

	Angiographic CMO‡ (n=7 eyes)			*Clinical CMO§ (n=15 eyes)*		
	No DR (n=6)*	*DR† (n=1)*	*Total (n=7)*	*No DR (n=3)*	*DR (n=12)*	*Total (n=15)*
Visual acuity	*No (%)*					
≥6/12	5 (83)	1 (100)	6 (86)	2 (67)	3 (25)	5 (33)
6/15–6/30	3 (17)	–	1 (14)	1 (50)	9 (75)	10 (67)
<6/30	–	–	–	–	–	–

*No diabetic retinopathy.
† Diabetic retinopathy.
‡Angiographic CMO only.
§Ophthalmoscopic and angiographic appearance of CMO.

existing diabetic retinopathy where 75% of patients achieved vision of only 6/15 to 6/30. Thus the visual prognosis in patients with clinical CMO is worse than in those with angiographic CMO. In eyes with no pre-existing diabetic retinopathy angiographic CMO was more common than clinical CMO (21% *v* 11%, Table 2). It resolved spontaneously with 1 year, it persisted only slightly more frequently than in the general population (7% *v* 4%), and its final visual acuity was good. In contrast, eyes with pre-existing diabetic retinopathy were more likely to develop clinical CMO (75% *v* 6%, Table 2), which has a relatively high tendency (56%) to persist for more than 1 year of follow-up.

Questions arise as to whether the lens implant increases the inflammatory reaction in the eyes of diabetic patients relative to those of non-diabetic patients, and whether diabetic patients with lens implants have more macular oedema than those without them. Many authors believe nowadays that diabetic patients need not be excluded from the optical advantages of intraocular lenses especially as in diabetics the optical disadvantages of peripheral field constriction and distortion with aphakic spectacle correction are intensified in the presence of macular disease and panretinal photocoagulation.[16] Correction by contact lens in diabetic patients is often complicated by recurrent corneal erosion.[17] These questions should be addressed in randomised clinical trials of cataract surgery with and without intraocular lens implantation in diabetic and non-diabetic patients.

The results of this study indicate that after cataract surgery with lens implantation CMO occurs more often and persists for longer in eyes of diabetic than of non-diabetic patients. In addition it is affected by the preoperative retinal status. Eyes with no pre-existing diabetic retinopathy tend to develop angiographic rather than clinical CMO; this seldom persists for longer than 1 year and the final visual outcome resembles that of the general population. In contrast operated eyes with pre-existing diabetic retinopathy tend to develop clinical CMO, which quite often persists for at least 1 year, and the final visual acuity can be expected to be in the range of 6/15–6/30. These findings may act as guidelines when cataract surgery is contemplated for diabetic patients. We would counsel a cautious approach for eyes with pre-existing diabetic retinopathy; surgery should probably not be recommended in such cases until vision has deteriorated to at least 6/30–6/60.

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British Journal of Ophthalmology, 1992, 76, 225–227

Ophthalmic pain following cataract surgery: a comparison between local and general anaesthesia

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Accepted for publication
13 September 1991

Abstract

Ophthalmic pain following uncomplicated extracapsular cataract surgery was assessed postoperatively in 61 patients; 55% undergoing ophthalmic surgery had no pain or discomfort postoperatively, and 32% reported slight discomfort. Approximately 8% of patients reported mild pain and the remaining 5% experienced moderate to severe pain. Local anaesthesia was shown to be more comfortable postoperatively than general anaesthesia in the immediate postoperative period with both groups receiving similar amounts of postoperative analgesics.

The actual appreciation of pain is both subjective and personal to the individual patient. Pain relief following ophthalmic surgery is often prescribed by one profession, assessed and administered by another often with the prescriber having little or no notion of what the patients are actually suffering except the belief that patients are not in pain unless they complain and that perhaps pain is an inevitable consequence of surgery. This study provides an estimate of the levels of postoperative pain encountered in ophthalmic patients which can be compared with other types of surgery measured on a similar standard pain scoring scale.

Table 1 Verbal descriptive pain scoring

0=no pain or discomfort
1=slight discomfort that is tolerable
2=mild pain that would require relief by 'pain-killers'
3=moderate pain that would require relief by 'pain-killers'
4=severe distressing pain requiring urgent relief by strong 'pain-killers'

Table 2 Linear analogue pain scoring in millimetres

No pain |______________________________| Max pain

Table 3 Nurse or patient's own assessment of anxiety

0=calm, relaxed, not worried
1=anxious, slightly worried about operation
2=very anxious, worried about operation

Table 4 Pain scores

	Number of patients		
	Day of return to ward	*1st post-op day*	*2nd post-op day*
Score 4	3	0	0
Score 3	2	1	2
Score 2	3	8	4
Score 1	19	21	19
Score 0	34	31	36

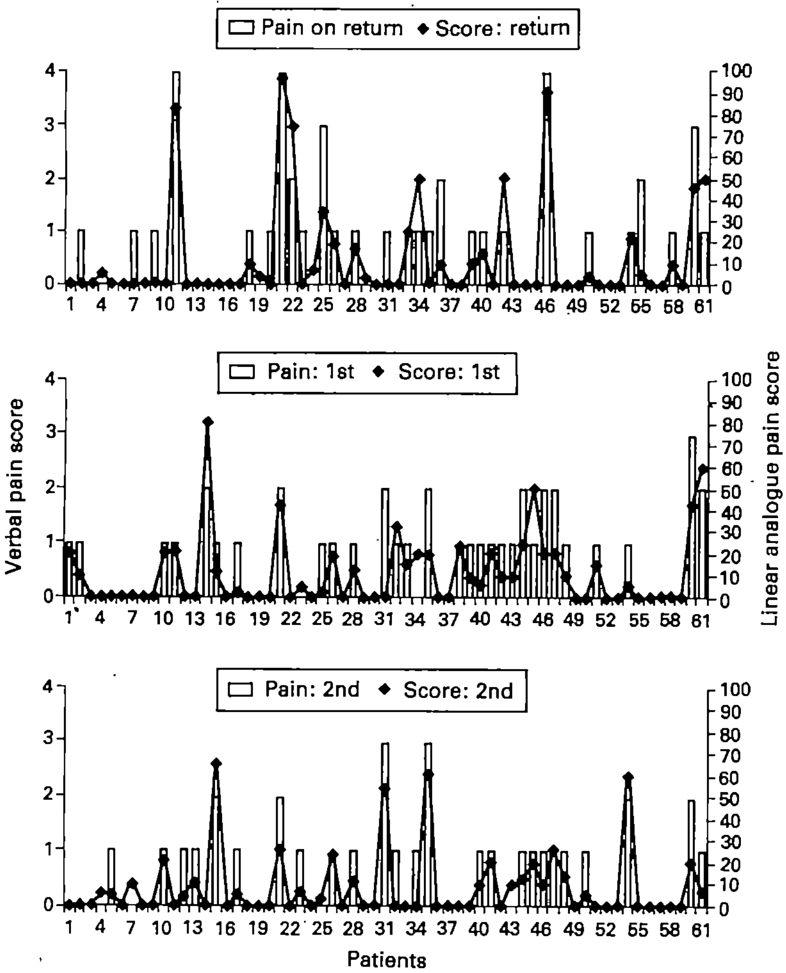

Figure 1 Levels of pain following cataract surgery on day of return to ward (top), first postoperative day (middle), and second postoperative day (bottom).

Method

Seventy one patients (65% females, 35% males) with a mean age of 67 years (SD 16) undergoing extracapsular cataract extractions were consecutively recruited into the study. Assessment of any ocular pain before operation was performed and four patients with pre-existing pain were excluded. The level of pain was quantified by a verbal descriptive scale from 0 to 4 (Table 1) and also on a linear analogue scale of 0 to 100 (Table 2).[1 2 3] Preoperative assessment also included the patients' assessment of their own anxiety level and the nurse assessment of the patients' anxiety level; both using the same verbal anxiety scoring from 0 to 2 (Table 3). The patients were also asked to score the level of pain they expected after their operation using the same verbal descriptive pain scoring system. Details of premedications and local anaesthetic type were noted. The extracapsular cataract extractions with intraocular lens (IOL) implants were performed by 16 different surgeons from registrar to consultant grades.

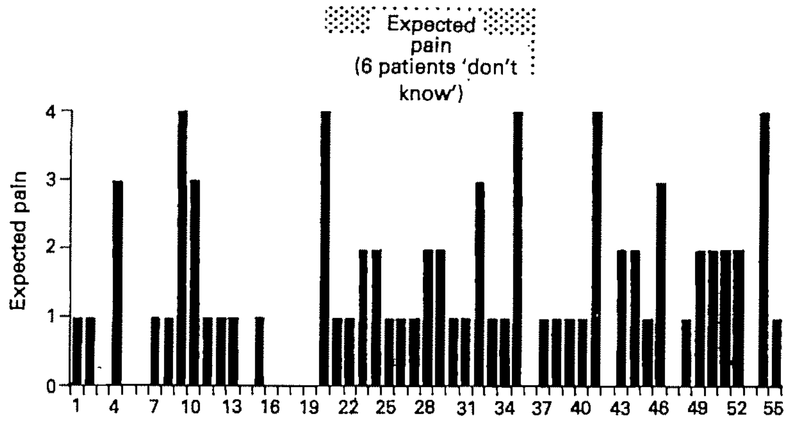

Figure 2 Level of expected pain in patients following cataract surgery.

Pain scores were assessed on return to the ward as soon as the patient was able to cooperate on the day of the operation and in the afternoon of the first and second postoperative day between 2 pm and 4 pm in the afternoon. Nurse assessment of the patient's anxiety level using the same verbal anxiety scoring from 0 to 2 had been obtained on each of the postoperative day. All postoperative complications were recorded and six patients with complications such as corneal abrasions, ocular hypertension requiring intervention and severe iritis were excluded because of possible contribution to postoperative pain. All patients received paracetamol as required with stronger analgesics when necessary. All analgesics dispensed both in theatre by the anaesthetists and in the wards by the nurses for each day were documented.

Results

The results of the verbal and linear analogue pain scores of 61 uncomplicated extracapsular cataract extractions are shown in Figure 1 and Table 4. There was no significant difference between the pain scores obtained on the day of operation, the first, and second postoperative days. The level of expected pain (Fig 2) was higher than the actual pain scored subsequently in our patients but there is no statistically significant relationship between expected and actual pain scores.

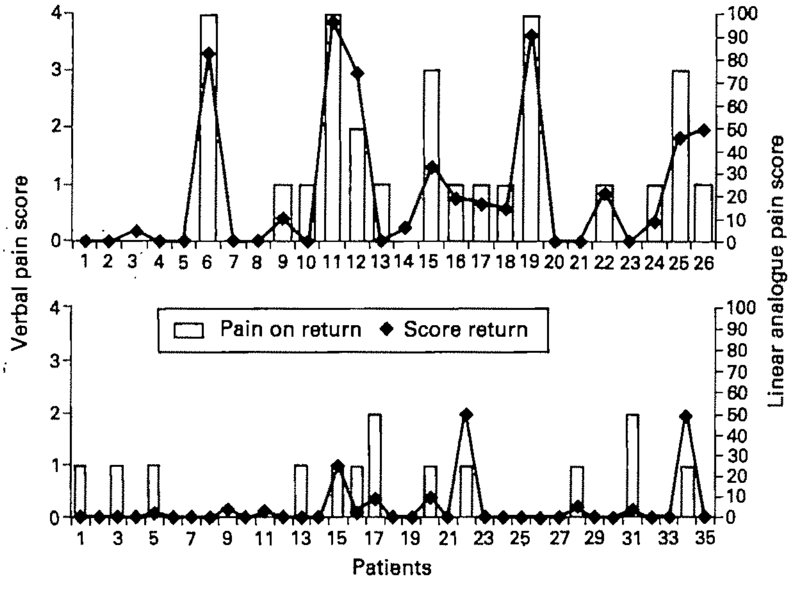

Figure 3 Levels of pain following cataract extraction with general anaesthesia (top) and local anaesthesia (bottom) on day of return to ward.

The pain scores of 35 patients under local anaesthesia and 26 patients under general anaesthesia on the day of cataract surgery are illustrated in Figure 3. The level of pain scored was significantly less in the local anaesthesia group compared with the general anaesthesia group both on verbal and on linear analogue scales with p=0·018 and p=0·003 respectively (Wilcoxon signed rank test). Analgesic consumption of paracetamol was also lower in the group having local anaesthetic cataract extractions (mean of 1·4 g of paracetamol) compared with the general anaesthetic (mean of 2·5 g of paracetamol) although this was not statistically significant (p=0·20, Wilcoxon signed rank test).

Discussion

The results show that in the studied patients about 55% undergoing ophthalmic surgery have no pain or discomfort postoperatively and approximately 32% reported slight discomfort. However approximately 8% of patients reported mild pain and the remaining 5% experienced moderate to severe pain while on analgesics prescribed when required. There appears to be a small group of patients who may be suffering unnecessarily and may not in fact request analgesics. These patients could benefit from regular dispensing of analgesics.

Patients having local anaesthesia for cataract extraction in this study are more comfortable postoperatively on the day of the operation and require less analgesia. It is of interest that our findings are supported by a German study on postoperative pain. Schaffer and his colleagues in 1988 found that postoperative pain following intraocular surgery was significantly higher after general anaesthesia compared with local anaesthesia with no difference in analgesic therapy in both groups.[4]

One possible explanation for this is that the patients undergoing local anaesthesia are in fact a different population group being older and perhaps less anxious. The mean age of local and general anaesthetic groups of patients were however similar (71·8 and 72·6 years respectively). Although the mean anxiety scores of the general anaesthetic patients were higher than those of the local anaesthetic patients (1·0 and 0·38 respectively) with p=0·07 (Wilcoxon signed rank test) before the operation, those obtained after the operation were similar (0·5 and 0·2 respectively) with p=0·5 (Wilcoxon signed rank test). This suggests that while general anaesthetic patients were apparently more anxious than local anaesthetic patients before the operation, after their operation there was no difference in their anxiety levels to account for the difference in postoperative pain levels.

As the average analgesic consumption was similar in both the general and local anaesthetic groups (1·8 g and 1·7 g of paracetamol) respectively on the day of return to the ward, with only one general anaesthetic case receiving the opioid analgesic Omnopon (papaveretum) 10 mg intramuscularly, the patients undergoing local anaesthesia for cataract extraction are probably more comfortable postoperatively because of the residual effects of the local anaesthetic agent itself. In all cases, lignocaine 2% with 1:200 000 adrenaline was used as the local anaesthetic agent which may have effects beyond 1 hour, providing patients with useful postoperative analgesia.

The effects of premedication may also contribute to local anaesthesia being more comfortable, with 84% of the local anaesthetic patients receiving Omnopon 10 mg and the sedating antihistamine Phenergan (promethazine hydrochloride) 50 mg 1 hour preoperatively. The premedication for general anaesthesia consists of either diazepam 10 mg or temazepam 10 mg without any analgesia in all cases.

Our findings suggests that there may be a case for administering topical anaesthetic agents to the eye or analgesics for all the general anaesthetic patients before they leave theatre and that regular administration of a mild analgesic, such as paracetamol, in all patients may reduce the overall pain and discomfort in both groups of patients.

We would like to thank Dr B Fleck and Dr B Dhillon for reviewing the manuscript.

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British Journal of Ophthalmology, 1992, **76**, 228–231

The course of diabetic retinopathy following cataract surgery in eyes previously treated by laser photocoagulation

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Accepted for publication
27 September 1991

Abstract

The course of diabetic retinopathy following extracapsular cataract extraction with posterior chamber lens implantation in eyes previously treated by laser photocoagulation for diabetic retinopathy was retrospectively studied in 33 eyes (33 patients). In 20 eyes (61%) there was no change in the retinal status postoperatively. In 13 (39%) there was postoperative progression of diabetic retinopathy compared with the fellow non-operated eye, in which progression occurred in nine eyes (27%). The severity of the preoperative status affected the incidence of progression. Four eyes (12%) developed complications of diabetic retinopathy – that is, rubeosis iridis and vitreous haemorrhage – which regressed after lasering. Cystoid macular oedema developed in 13 eyes (39%) and its incidence varied according to the postoperative course of diabetic retinopathy. The majority of the eyes showed a postoperative improvement in vision.

A number of studies have shown that diabetic retinopathy may progress after cataract extraction.[1-11] In our earlier study of the course of diabetic retinopathy following cataract extraction we found that the preoperative presence of diabetic retinopathy is a risk factor for its postoperative progression.[10] Excluded from that study however were eyes that, prior to surgery, had received laser treatment for established diabetic retinopathy. It was of interest to find out whether the preoperative laser treatment in those eyes had affected the postoperative course of diabetic retinopathy. In order to address this question we retrospectively reviewed the course of diabetic retinopathy in diabetic eyes that underwent extracapsular cataract extraction and in which the retinopathy had been treated by laser treatment at least 3 months prior to the cataract surgery.

Patients and methods

The records of all diabetic patients who underwent extracapsular cataract extraction with posterior chamber intraocular lens implantation in our department between the years 1984 and 1990 were reviewed. Included in this study were 33 eyes of 33 patients who met the following criteria: (1) diabetes mellitus diagnosed at least 6 months prior to cataract surgery; (2) uneventful surgical procedure on one eye only; (3) no other ocular disorders; (4) laser treatment for established diabetic retinopathy applied at least 3 months before surgery. The laser treatment had consisted of panretinal photocoagulation for proliferative or very severe non-proliferative diabetic retinopathy and/or focal or grid argon green laser photocoagulation for macular oedema. Thus all of the patients had been diagnosed as having either advanced non-proliferative or proliferative diabetic retinopathy; (5) a postoperative follow-up period of at least 1 year; (6) a fundal examination prior to or within 3 days after surgery as a baseline examination for future comparison with the postoperative retinal course; (7) at least one additional fundal examination during three distinct periods within the first year of follow-up. The first follow-up period, F1, was from the beginning of the second week after surgery to the end of the third month. The second, F2, was between 4 and 6 months after surgery, and the third, F3, was between the seventh and the twelfth month.

For each patient a standardised medical protocol was completed, giving detailed demographic and clinical information including duration of diabetes mellitus, presence of other systemic diseases, and medications. During each follow-up period the ocular findings were recorded. These included best corrected visual acuity, applanation tonometry, biomicroscopy, Goldman three-mirror examination, and indirect ophthalmoscopy. Also recorded were the findings of postoperative fluorescein angiography and the results of laser treatment applied during the follow-up periods F1 and F3. Fundal examinations, colour fundus photographs, and fluorescein angiography readings were performed by a retinal specialist.

On the basis of the diabetic retinal findings two groups were identified. The first, defined as the 'no change' group, consisted of eyes in which no postoperative aggravation of diabetic retinopathic changes was observed. The second, termed the 'progression' group, consisted of eyes in which diabetic retinopathy progressed following surgery. Progression was considered to have occurred when: (1) after surgery a patient with pre-existing non-proliferative diabetic retinopathy (NPDR) showed postoperative aggravation of the non-proliferative changes with or without the occurrence or aggravation of cystoid macular oedema (CMO) or showed development of proliferative diabetic retinopathy (PDR); or (2) a patient with PDR showed postoperative recurrence of proliferative changes or development of non-proliferative changes in the posterior pole, with or without the occurrence or aggravation of CMO. The postoperative occurrence of CMO alone without other evidence of aggravation of diabetic retinopathy was not regarded as progression of retinopathy since CMO is a

Table 1 Clinical features of patients with and without progression of diabetic retinopathy following cataract surgery

	*No change** *(n=20 cases)* *(61%)*	*Progression†* *(n=13 cases)* *(39%)*
Mean age (SD) (range), years	68 (7) (42–80)	61·4 (8) (32–80)
Mean duration of DM‡ (SD) (range), years	17·3 (8) (1–30)	16·4 (6) (10–30)
	No of patients (%)	
Male/female	12:8 (60:40)	6:7 (46:54)
Management of DM		
Diet	–	–
Oral agents	12 (60)	5 (38)
Insulin/insulin and oral	8 (40)	8 (62)
Vascular disease:		
Hypertension	8 (40)	4 (31)
Cardiac	2 (10)	1 (8)
Hypertension and cardiac	2 (10)	2 (15)
Other	5 (25)	3 (23)

*Without postoperative progression of diabetic retinopathy.
†With postoperative progression of diabetic retinopathy.
‡Diabetes mellitus.

known complication after cataract surgery even in the absence of diabetic retinopathy.

The χ^2 test was used for statistical analysis.

Results

Of the 33 patients 18 were men and 15 were women. The mean age at the time of surgery was 64·7 years (range 32 to 80 years) and the mean duration of diabetes mellitus was 16·9 years (ranging from 1 to 30 years). Prior to surgery 22 eyes had NPDR, of which seven also had CMO, and 11 eyes had PDR, one of them with CMO.

Following cataract surgery 20 eyes (61%) showed 'no change' in retinal status and 13 (39%) showed 'progression' of diabetic retinopathy. In the no change group, although none showed postoperative aggravation of diabetic retinopathy, CMO development was observed in five eyes, three of them with NPDR and two with PDR. In the progression group only one eye with preoperative NPDR developed PDR after surgery, and this progression was accompanied by CMO. Following cataract surgery six eyes in which PDR had been treated preoperatively by laser photocoagulation developed new areas or progression of neovascularisation. Of these eyes two developed vitreous haemorrhage, one developed rubeosis iridis, and one developed both rubeosis iridis and vitreous haemorrhage. In the group of 13 eyes that showed postoperative progression of retinopathy eight eyes, five with NPDR and three with PDR preoperatively, developed CMO as well. Thus a total of 13 eyes which initially did not have CMO developed it after cataract surgery.

Table 1 compares the clinical features of patients with and without postoperative progression. Differences between the two groups were not significant, although more patients with progression than with no change were on insulin treatment for the management of diabetes.

Correlation between the preoperative status of diabetic retinopathy and its postoperative course revealed that of 22 eyes with preoperative NPDR the postoperative retinal status remained unchanged in 15 (68%) and progressed in seven (32%). Of 11 eyes with preoperative PDR the postoperative retinal status remained unchanged in five (45%) and progressed in six (55%).

Of the 13 eyes with postoperative progression of diabetic retinopathy seven had NPDR and six had PDR. Among the former group progression of retinopathy occurred in five eyes in the F1 period, in one eye in the F2 period, and in one eye in the F3 period. In the latter group progression occurred in one eye in the F1 period, in three eyes in the F2 period, and in two eyes in the F3 period.

Of 13 eyes with postoperative evidence of progression of diabetic retinopathy, 10 received additional laser treatment within 1 year of cataract surgery, because of the following indications: retinal neovascularisation (two eyes), rubeosis iridis (one eye), vitreous haemorrhage (one eye), rubeosis iridis and vitreous haemorrhage (one eye) and aggravation of NPDR (five eyes). Following laser treatment the five eyes with PDR showed resorption of vitreous haemorrhage and regression of rubeosis iridis and retinal neovascularisation. In the other five eyes with NPDR one eye showed an improvement in the retinal status, three showed no further changes, and one showed further progression of the retinopathy in spite of treatment. Three eyes were not treated; in two of them (with NPDR) the retinopathy remained stable and in one eye (with PDR) it deteriorated with development of vitreous haemorrhage towards the end of the 1 year period of follow-up. The latter was treated successfully after the end of the 1 year period of follow-up.

Good visual acuity of 6/12 or better was achieved in only 24% of the study group (Table 2). However, a comparison between the pre- and postoperative visual acuity revealed that the majority of eyes showed at least some improvement (Fig 1). The most frequent cause of the low visual acuity was the presence of CMO (Table 3).

Follow-up of the 33 non-operated fellow eyes over 1 year revealed no change in the retinal status of 24 (73%) of them and progression of diabetic retinopathy in nine (27%). Among the former group retinopathy remained unchanged in 17 of the fellow operated eyes (71%) and progressed in seven (29%). Among the latter group retinopathy progressed in six of the fellow operated eyes (66·6%) and remained unchanged in three (33·3%). A symmetric course was seen in 23 patients (70%).

Discussion

Postoperative progression of diabetic retinopathy occurred in 39% of the eyes in this series. This rate is similar to that in diabetic eyes that underwent the same surgical procedure but did not receive laser treatment prior to surgery (38%),[10] and is slightly higher than that among the fellow non-operated eyes (27%). Furthermore when we examined the state of retinopathy in non-operated eyes in relation to the postoperative course in the fellow operated eyes we found that where the operated eye showed no change in retinal status the non-operated eye tended also to remain unchanged (71%), while if the operated eye showed progression there was a tendency to progression in the non-operated eye as well (66·6%).

Ruiz and Saatci also found progression of

Table 2 Final visual acuity results at the end of 1 year of postoperative follow-up

	No change (n=20 eyes)*		*Progression† (n=13 eyes)*		
Visual acuity	*Without CMO‡ (n=10)*	*With CMO (n=10)*	*Without CMO (n=2)*	*With CMO (n=11)*	*Total (n=33) No. (%)*
≥6/12	3	1	–	4	8 (24)
6/15–6/30	–	5	–	3	8 (24)
<6/30	7	4	2	4	17 (52)

*Without postoperative progression of diabetic retinopathy.
†With postoperative progression of retinopathy.
‡Cystoid macular oedema.

Table 3 Reasons for poor visual acuity (less than 6/12)

	No change (n=16)*	*Progression† (n=9)*
Cystoid macular oedema	8	7
Diabetic maculopathy	3	
Vitreous haemorrhage	2‡	1
Optic atrophy	2	1
Opacification of posterior capsule	1	

*Without postoperative progression of diabetic retinopathy.
†With postoperative progression of retinopathy.
‡Vitreous haemorrhage present prior to cataract surgery.

diabetic retinopathy after extracapsular cataract extraction and posterior chamber lens implantation in eyes with laser-ablated retina.[11] Nevertheless the results of our study appear to indicate that preoperative laser treatment of eyes with advanced retinopathy attenuates the postoperative retinopathy course. This may be inferred from the following findings: (1) the rate of postoperative progression in eyes with advanced preoperative diabetic retinopathy did not differ significantly from the fellow non-operated eyes; (2) the course of progression in many of the non-operated eyes resembled that in the operated fellow eye; (3) the rate of postoperative progression in eyes treated with laser for advanced preoperative diabetic retinopathy was similar to that in eyes with mild diabetic retinopathy.[10]

The overall incidence of postoperative progression of diabetic retinopathy was 39%. The rate varied however according to the preoperative severity of the retinopathy, from 32% (7/22) in eyes with preoperative NPDR to 55% (6/11) in eyes with preoperative PDR. This is in line with previous observations that the postoperative prognosis of diabetic retinopathy depends on its preoperative severity.[7 10] Deterioration usually took the form of aggravation of a pre-existing state, either of NPDR or of PDR, and only one eye showed progression from NPDR to PDR. When progression developed in eyes with preoperative NPDR it was evident usually within 3 months of surgery. In eyes with preoperative PDR, aggravation of retinopathy tended to appear more than 3 months after surgery.

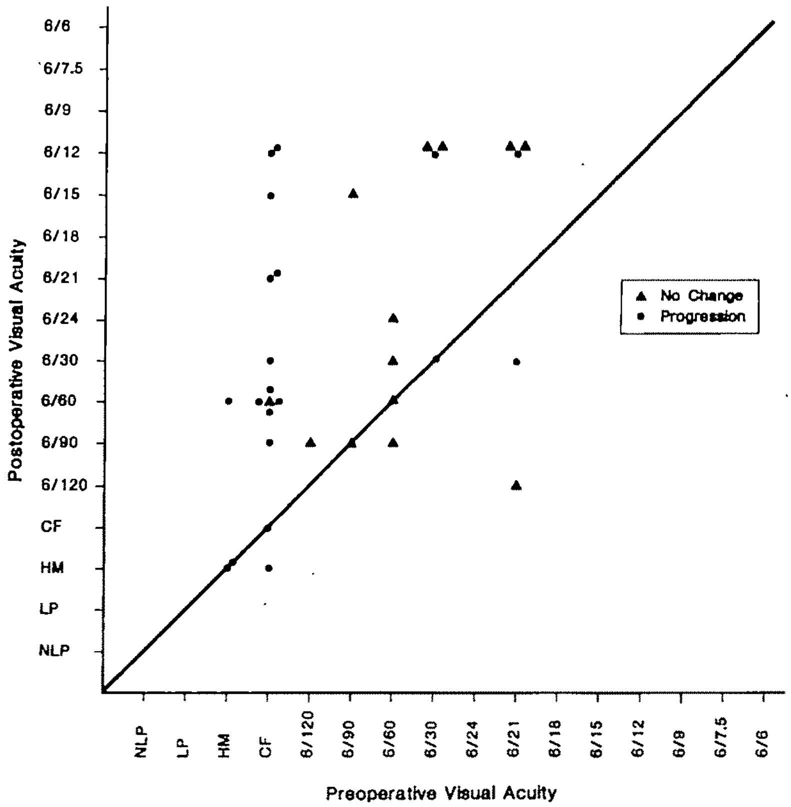

Figure 1 Scattergram of best corrected visual acuity before cataract surgery and at 1 year of follow-up. (▲) No change=eyes without postoperative progression of diabetic retinopathy. (●) Progression=eyes with postoperative progression of retinopathy. NLP=no light perception; LP=light perception; HM=hand movements; CF=counting fingers.

Cystoid macular oedema often occurred after surgery, and new cases of CMO were seen in 13 eyes (39%); its incidence varied, however, with the postoperative retinal course. It developed even in 25% (5/20) of eyes without postoperative aggravation of retinopathy, and in as many as 61·5% (8/13) of eyes with postoperative retinopathic progression. Cheng and Franklin[7] also found that CMO occurs more frequently in eyes with diabetic retinopathy than without it, whereas Ruiz *et al*[11] found only an 8% incidence of CMO development following extracapsular cataract extraction.

Of the 13 eyes in the present series that showed progression of retinopathy six exhibited aggravation of PDR; of these four developed PDR-associated complications including vitreous haemorrhage and rubeosis iridis. None of the eyes progressed to neovascular glaucoma. Interestingly all of the eyes with complications of PDR had already developed them prior to surgery; in all cases the complications regressed after lasering but reappeared following surgery. In three eyes they disappeared again after additional laser treatment during the year of follow-up; in the fourth, vitreous haemorrhage appeared towards the end of the study period and its outcome is therefore not recorded here. The inclusion of eyes with advanced diabetic retinopathy may explain the occurrence of complications in this group in spite of preoperative lasering, especially the development of rubeosis iridis in two eyes. In a previously described non-lasered group[10] these complications, although expected, did not occur even though that series – unlike the present one – included eyes that underwent intracapsular cataract extraction considered as a risk factor for development of rubeosis.[4 12 13] On the other hand the diabetic retinopathy in those eyes was less advanced on average than in the present series.

Visual acuity of at least 6/12 was achieved in 24% of our patients, and an additional 24% achieved vision between 6/15 and 6/30. In eyes with severe diabetic retinopathy, and especially in those with maculopathy, improvement in vision may be a more relevant criterion of success than the final visual acuity. As shown in Figure 1 a majority of eyes showed improvement in vision postoperatively even though many of these eyes had advanced diabetic retinopathy and CMO occurred frequently (Table 3).

The results of this study indicate that in eyes with advanced diabetic retinopathy laser treatment applied at least 3 months prior to cataract surgery may stabilise the retinopathy but does not prevent its postoperative progression. The question then arises: should patients with cataract but with adequate fundus visualisation receive laser treatment even when the diabetic retinopathy is not severe enough to meet the criteria for laser treatment outlined by the Diabetic Retinopathy Multicentre Studies? Until this issue is tested in randomised clinical trials we suggest that these patients be closely followed after cataract surgery and any progression of their retinopathy be treated promptly.

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British Journal of Ophthalmology, 1992, 76, 232–234

Strampelli's osteo-odonto-keratoprosthesis. Clinical and histological long-term features of three prostheses

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Accepted for publication 29 August 1991

Abstract

The histological features are reported of osteo-odonto-acrylic laminae removed from three patients who for differing underlying causes received Strampelli's osteo-odonto-keratoprostheses (OOK) 20, 16, and 12 years previously. It appears that preservation of the alveolar-dental ligament plays a definitive role in the maintenance of the prosthesis. If this tissue undergoes necrosis as a consequence of an inflammatory disease the implanted material is eventually lost. However when no such event occurs the OOK is well preserved and well tolerated even 20 years after implantation.

Osteo-odonto-keratoprosthesis (OOK) constitutes a valid option in the management of patients with opaque corneas in whom penetrating keratoplasty is not feasible.[1-8] This technique was developed by Strampelli in 1963[9] and is now well recognised despite being, wrongfully in our opinion, unduly neglected. Indeed this prosthesis has stood the test of time although the complexity of the surgical technique does represent a disadvantage.

The removal of three prostheses 20, 16, and 12 years, respectively, after implantation for different causes has allowed us to investigate the preservation status of the osteodental laminae after prolonged periods.

Patients

CASE 1

The male patient aged 54 years had suffered from bilateral corneal opacities due to lime burn since 1960. In 1968 bilateral OOK was performed. In the right eye a small incisor tooth was used to support the optical device. Because of the smallness of the tooth the fixed lens could only be 1·75 mm in diameter. Postoperative visual acuity was 1/10 and remained so for 20 years after implantation when the right osteo-odontoacrylic lamina (ODAL) was removed and a new one, provided with a larger lens (2·75 mm), was implanted. After this second operation visual acuity improved to 5/10. The ODAL in the left eye was still in position but visual potential had been lost because of secondary glaucoma.

CASE 2

In 1970 a male patient, aged 50 years, lost the whole left eye and the right eye cornea became opaque as the result of alkali burns. In 1973 a right OOK was successfully performed with a postoperative visual acuity of 6/10. The clinical course was unremarkable until the beginning of 1988 when the right eye was affected by repeated inflammatory episodes which did not regress after the administration of broad spectrum antibiotic therapy and anti-inflammatory agents. Due to this complication the patient's visual acuity had decreased to only light perception. Finally 1 year after the onset of the ocular inflammation the lamina had to be removed because of the development of a mucosal ulcer and a white dense membrane behind the implant.

CASE 3

The patient was a 46-year-old female suffering from Hallerman-Streiff syndrome since birth with bilateral blindness. In 1978 a left OOK was performed leading to no substantial visual improvement. In January 1990 acute inflammation of the periprosthetic tissues occurred which did not respond to treatment. Two months later, with the symptoms persisting and the visual acuity not having recovered, the prosthesis was removed and sent for histological examination.

Pathology

The ODALs thus obtained were fixed for 24 hours with 4% buffered formalin and glycol methacrylate embedded with no prior decalcification. Sections of 1–2 μm were cut with a carbon tungsten knife and stained either with routine methods (haematoxylin-eosin, azur II methylene blue, May-Grunwald-Giemsa) or with histochemical methods (PAS for glyco-

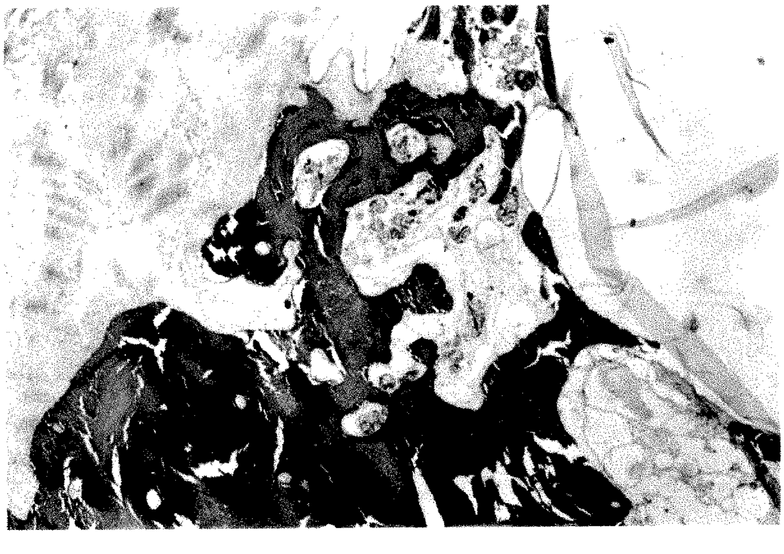

Figure 1 Mature bone and medullary cavities containing aggregates of pigmented cells circumscribe the site of lens. (Haematoxylin and eosin, ×23.)

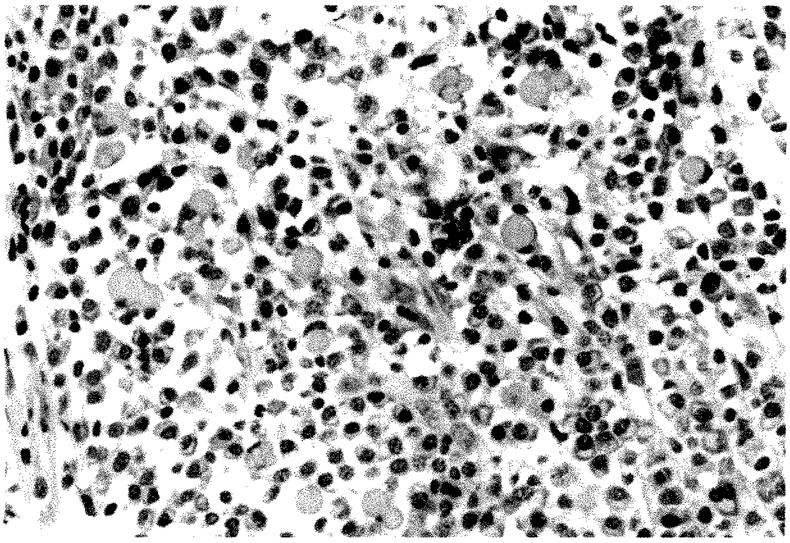

Figure 2 Alveolar dental ligament is replaced by a chronic inflammatory tissue. Mononuclear phagocytes with eosinophilic globules in the cytoplasm are seen. (Haematoxylin and eosin, ×90.)

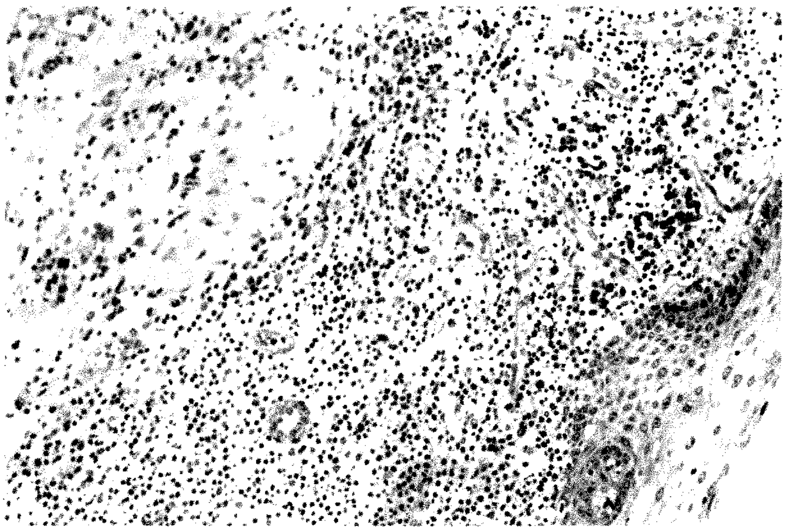

Figure 3 Chronically inflamed alveolar dental ligament lined by non-keratising squamous epithelium. (Haematoxylin and eosin, ×23.)

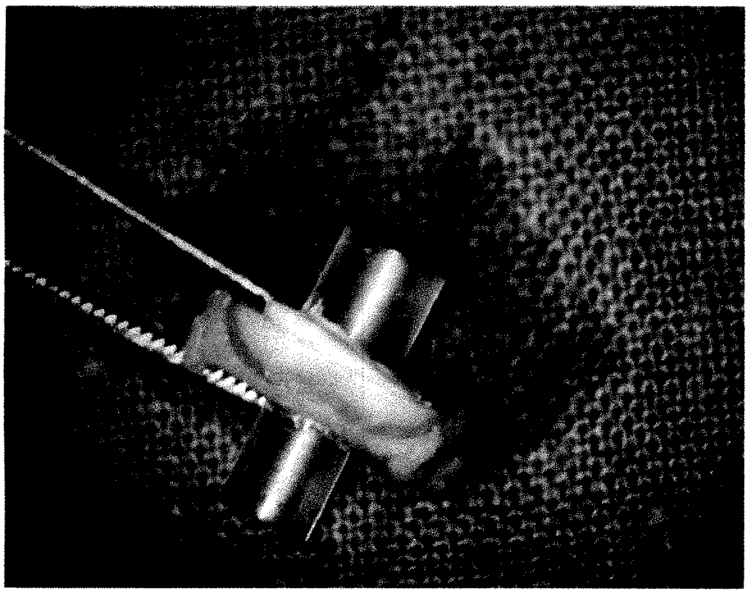

Figure 4 Strampelli's osteo-odonto-keratoprosthesis.

proteins, Masson Fontana for melanin and Perl's for iron).

Sections obtained from the ODAL removed after a 20-year period (case 1) showed predominantly mature lamellar bone with minimal immature woven bone. Focal moulding characterised by inactive lacunar and marginal resorption and lack of osteoclasts and osteoid tissue were present. Fragments of dental tissue were connected to the bone by fibroligamental tissue. Bone and tooth circumscribed an optically empty hole presumed to have contained the lens (Fig 1). Neither necrotic nor inflammatory foci were seen in these tissues. However in the medullary cavities numerous mast cells at the periperiosteal site were observed as well as aggregates of large cells with round nuclei and voluminous cytoplasm containing brown granules that proved positive when submitted to Fontana staining. Free pigment granules were also detected in adjacent tissues.

The inflamed ODAL removed after 16 years of implantation (case 2) was devoid of bone which had broken into pieces during removal. Microscopically the tooth displayed no morphological alterations. However next to it a chronic inflammatory reaction was observed, mainly consisting of plasma cells and lymphocytes, that was almost totally surrounded by non-keratinising squamous epithelium (Fig 2). This epithelium having focally penetrated the inflammatory tissue showed multiple areas of ulceration in which necrosis and polymorphonuclear leucocytes were seen. Interspersed within the chronic inflammatory cells were a few mononuclear phagocytes showing one or more eosinophilic PAS-negative anisometric globules in the cytoplasm. Occasionally similar globules could be observed in the extracellular matrix.

Histological sections obtained from the third patient were composed of dentine, woven bone, and soft tissues. Normal dentine prevailed; it showed a central round aperture where the lens was located. In the contiguous totally viable bone tissue physiological resorption activity was evident. Bone was partially covered by non-keratinising squamous epithelium with focal interposition of chronic mononuclear infiltrate rich in plasma cells. Around the tooth there was well vascularised and chronically inflamed fibrous connective tissue partially lined by non-keratinising squamous epithelium (Fig 3). Among the inflammatory cells numerous mast cells were present.

Discussion

The operative technique is certainly complex inasmuch it involves the performance of different operations which take up a period of 6 to 12 months. The optical device consists of a 3 mm thick lamina obtained from a tooth root and alveolar dental ligament of the patient; an acrylic lens is inserted in the lamellar section (Fig 4). The OOK technique has been described previously in detail.[4 8 9]

Briefly, Strampelli's OOK offers three advantages over the alloplastic prostheses: (1) permanent fixation of an acrylic lens; (2) insertion of the mucosal epithelium onto the alveolar dental ligament; (3) long-term retention of the prosthesis due to its complete biological compatibility as far as other pathological conditions do not occur.

As the anterior surface of the ODAL protrudes over the surrounding tissues epithelial proliferation is stimulated. However when the epithelium reaches the alveolar dental ligament the proliferation ceases. In this way the lens will not be covered by a membrane and the epithelium will not proliferate behind the optical cylinder to promote fistula formation, secondary intraocular infection, hypotone, uveitis, visual loss, and probable extrusion of the ODAL. Long-term retention of a keratoprosthesis mainly depends on whether it behaves as a graft or a simple implant. On the other hand mesoprostheses (like keratoprostheses) will not be retained unless a true biological connection is established with the tissue at the point at which it is inserted – namely the epithelium.

In the literature few authors have reported their direct experience with Strampelli's OOK[2 3 10] and some series related only to small numbers of cases.

Our series is composed of 75 patients on whom Strampelli operated between 1964 and 1975 and who have subsequently been controlled by the present authors; 86 additional operations were performed at our centre from 1968 to 1990. Of these six were performed in 1990. On the whole the incidence of ODAL necrosis was very low (3·8%) and was associated with loss of the alveolar dental ligament. In particular necrosis had occurred in only one out of 155 cases within the first 10 postoperative years while in five instances it occurred 10 to 20 years later. It seems that no rejection of the prostheses occurred because of the compatibility of the dental support.

However other potential causes of blindness should be noted especially secondary glaucoma unresponsive to medical or surgical therapy, fistula formation, and occasionally, retinal detachment.

Compared with Strampelli's OOK other kinds of keratoprostheses with synthetic support frames, in addition to the aforementioned complications, carry with them the risk of extrusion of the implant as retention is ensured only by pure mechanical contact.

Cardona refers to an extrusion rate of 21·3% with the through-and-through keratoprosthesis due to several causes[11]; other authors using the same technique confirm this possibility.[12-14] Moreover, with Choyce's two-piece perforating keratoprosthesis epithelial erosion around the optical cylinder is to be expected in 21·6% of cases.[15]

Some authors performing Strampelli's OOK report a high incidence of extrusion from an unspecified cause or visual loss due to secondary glaucoma and eye infection.[10] According to our experience and to the experience of other authors,[3] implant necrosis does not occur provided the tooth is correctly removed along with a viable alveolar dental ligament.

Biological tolerance of the ODAL was confirmed in our series by histological examination of three prostheses. The oldest one, in which the prosthesis was changed 20 years after implantation to provide a device carrying a larger optical cylinder, was microscopically still composed of viable and well preserved tissues. When tissues become inflamed or undergo necrosis the implant behaves like an allogeneic material and is eventually extruded. This possibility was demonstrated by histological examination of the second ODAL removed 16 years after implantation. In this instance the alveolar dental ligament was replaced by a chronic inflammatory tissue. Therefore it may be asserted that as long as the grafted tissue remains viable the prosthesis will stay in position. In the ODAL removed prophylactically 2 months after initial inflammation a viable alveolar dental ligament was present, although a moderate to intense chronic nonspecific surrounding infiltrate could be observed. Furthermore the dental and bone structures were uncompromised which suggests that long-lasting inflammation is necessary to cause necrosis of the prosthesis.

Strampelli's OOK is a surgical technique offering long-term guarantees of tolerance and steadiness and is the only prosthesis with more than 20 years follow-up. Nevertheless the development of an allogeneic keratoprosthesis capable of lasting as long as an OOK but easier to implant and less traumatic for the patient would be valuable. Some of the newer keratoprostheses appear promising,[16] although they need further experimentation on a long-term basis.

We are grateful to Professor A Garner for constructive criticism and to Miss Silvia Berni for the expert technical assistance.

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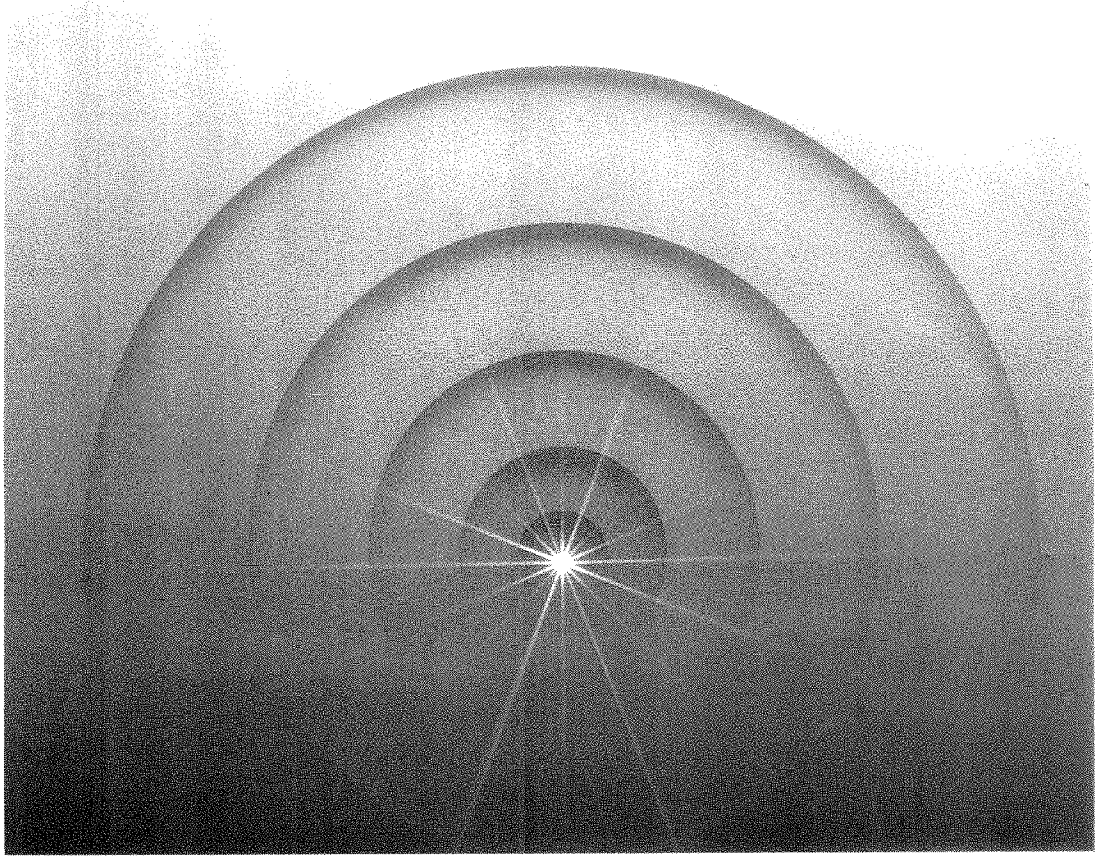

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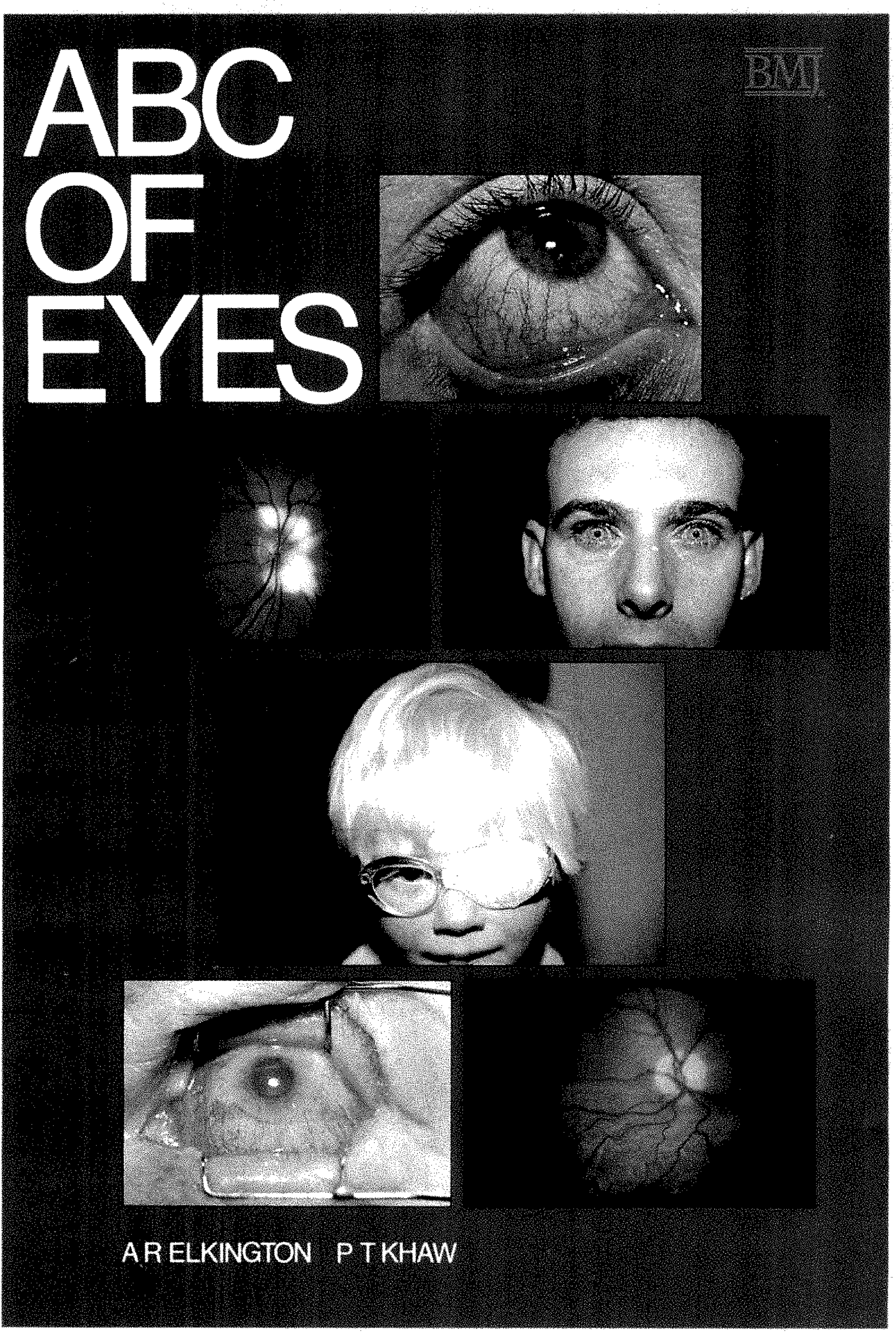

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British Journal of Ophthalmology, 1992, 76, 235–237

The role of preservatives in the conjunctival toxicity of subconjunctival gentamicin injection

M Pande, F Ghanchi

Abstract

Subconjunctival gentamicin was identified as the cause of conjunctival chemosis and capillary closure in a recent study conducted in this department. The gentamicin preparation used in the study contained preservatives. The current prospective study was set up to investigate the role of preservatives in the conjunctival toxicity of subconjunctival gentamicin. Seventy five patients undergoing cataract surgery were enrolled in the study. They were split into three groups of 25 each. Group A patients were given a subconjunctival injection of a preservative-free aqueous solution of gentamicin at the end of the cataract procedure. Group B patients were given a subconjunctival injection of gentamicin containing sodium metabisulphite and disodium edetate as preservatives at the end of the cataract procedure. Group C was the control group where patients were not given any subconjunctival injection. The incidence and severity of conjunctival chemosis were observed in the three groups. The difference between groups A and B patients who received preservative-free gentamicin and gentamicin with preservatives respectively was significant ($p<0.02$).

In a recent study conducted in this department subconjunctival gentamicin was identified as the cause of conjunctival capillary closure and chemosis.[1] Jenkins *et al* in 1990 reported similar manifestations of conjunctival toxicity of subconjunctival gentamicin.[2] In both these studies the gentamicin preparation (Cidomycin injectable, Roussel) used contained sodium metabisulphite, methyl hydroxybenzoate, propyl hydroxybenzoate and disodium edetate as preservatives. The role of these preservatives as causative or contributory factors in the conjunctival toxicity of gentamicin is not clear. This prospective study was set up to investigate the role played by preservatives in gentamicin toxicity. The above gentamicin preparation is widely used in the UK for subconjunctival injections but it is not recommended by the manufacturer for this use. The gentamicin preparations used in this study are both manufacturer-recommended preparations for subconjunctival use, one with preservatives and one preservative free.

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Accepted for publication 29 August 1991

Patients and methods

Seventy five eyes of 75 patients admitted for cataract surgery at the Hull Royal Infirmary from 20 December 1990 to 20 March 1991 were enrolled in the study. They had a mean age of 75·41 years with a range of 42 to 93 years. There were 35 male and 40 female patients.

Patients with a history of postoperative conjunctival chemosis, chemical burn, conjunctival trauma, and an abnormal conjunctival examination in the form of scarring or symblepharon were excluded from this study.

All patients were routine waiting list admissions and were sequentially allocated on admission into three groups of 25 each as follows.

GROUP A

Patients given a subconjunctival injection of 20 mg of gentamicin in 0·5 ml in the lower fornix at the conclusion of their cataract operation. The sterile aqueous injection was prepared from gentamicin sterile powder (Cidomycin sterile powder, Roussel, recommended by manufacturer for subconjunctival use[3]) in the hospital pharmacy and contained no preservatives.

GROUP B

Patients given subconjunctival injection of 20 mg of gentamicin in 0·5 ml (DBL Gentamicin injection, David Bull Laboratories recommended by manufacturer for subconjunctival use as per communication to hospital pharmacy) in the lower fornix at the conclusion of their cataract operation. This preparation contains sodium metabisulphite and disodium edetate as preservatives.

GROUP C

This was the control group and patients did not receive any subconjunctival injection at the conclusion of their cataract operation.

All patients underwent planned extracapsular cataract surgery under general anaesthesia. The conjunctival sacs were examined 24 hours postoperatively and the presence or absence of chemosis was noted. If present the severity was noted using the following criteria.

Grade 1 – involvement up to 30% of conjunctival area.

Grade 2 – involvement of 30% to 50% of conjunctival area.

Grade 3 – involvement of 50% to 100% of conjunctival area.

The observer was unaware of patient group allocation during patient examination.

Results

Table 1 shows the incidence of chemosis in the three study groups; 17 of 25 patients in group A and 24 of 25 patients in group B had chemosis

Table 1 *Incidence of chemosis in the study groups*

	Number of patients (%)		
Group	*Chemosis*	*No chemosis*	*Total*
A	17 (68·00)	8 (32·00)	25
B	24 (96·00)	1 (4·00)	25
C	0 (0·00)	25 (100·00)	25

Table 2 *Severity of chemosis in groups A and B**

	Number of patients (%)			
Group	*Grade 1†*	*Grade 2*	*Grade 3*	*Total*
A	10 (58·84)	6 (35·28)	1 (5·88)	17
B	5 (20·83)	9 (37·54)	10 (41·66)	24

*No patients had chemosis in group C.
†See text for chemosis grading criteria.

while no patients in the control group C had chemosis. The differences in the incidence in the groups clearly indicate the causative association of the two gentamicin preparations with chemosis and is significant at the 0·001 level using the χ^2 test. The difference in the incidence of chemosis between groups A and B indicate an increased incidence of chemosis with the preparation used in group B (with sodium metabisulphite and disodium edetate as preservatives) and is significant ($p<0·02$) using the χ^2 test.

Table 2 shows the severity of chemosis in patients from groups A and B. Of the 17 patients in group A who had chemosis, 10 had grade 1, six had grade 2, and one had grade 3 chemosis by the criteria used in this study. Of the 24 patients in group B who had chemosis, five had grade 1, nine had grade 2 and 10 had grade 3 chemosis by the criteria used in this study. Applying the χ^2 test the higher number of patients with grades 2 and 3 chemosis in group B is significant ($p<0·02$). This suggests that the preparation used in group B (with sodium metabisulphite and disodium edetate as preservatives) gives rise to a more severe chemosis compared with the preparation used in group A (preservative free).

Discussion

Conjunctival chemosis and capillary closure are the reported toxic manifestations of subconjunctival gentamicin.[1,2] Fortified topical gentamicin has been shown to cause conjunctival necrosis.[4] Corneal endothelial changes have been reported after subconjunctival gentamicin in rabbits.[5]

The cause of conjunctival gentamicin toxicity observed remains unclear. The intrinsic cytotoxicity of gentamicin has been demonstrated on kidney proximal tubules,[6] cultured cells obtained from various ocular structures,[7] and retinal pigment epithelial cells in rabbits.[8] Similar cytotoxicity has been reported in conjunctival fibroblasts in rats, rabbits, and humans after the subconjunctival injection of gentamicin.[9] Our results also demonstrate the intrinsic toxicity of gentamicin to the conjunctiva.

Clinical studies[1,2,10] raise the possibility of preservatives causing and contributing in the conjunctival toxicity of subconjunctival gentamicin. The gentamicin preparations used in these studies contained two or more of the preservatives sodium metabisulphite, methyl hydroxybenzoate, propyl hydroxybenzoate and disodium edetate. Snider *et al* have suggested that the preservatives mentioned above may cause or contribute to the toxic effects of gentamicin.[11] Our results clearly demonstrate the causative and contributory role of sodium metabisulphite and disodium edetate in the conjunctival toxicity of subconjunctival gentamicin injection.

The mechanism for the increased conjunctival toxicity of the gentamicin preparation containing sodium metabisulphite and disodium edetate could either be related to a change in the physical properties of the solution induced by these substances or to their intrinsic molecular structure.

An examination of their physical properties however did not reveal any significant difference in pH between the gentamicin preparation with preservatives (pH 3·9) and the preparation without preservatives (pH 4·2). The calculated osmolarity of the preservative-free preparation was 67·8 mosm/l and that of the preparation with preservatives was 143 mosm/l. Considering a solution with an osmolarity of approximately 300 mosm/l to be isotonic with blood and tears[12] both the preparations used in this study are significantly hypotonic. Conjunctival chemosis was the major manifestation of gentamicin toxicity indicating a fluid shift out of the conjunctival capillaries. The hypotonicity of both the preparations makes such a fluid shift highly unlikely. This is further substantiated by the fact that the observed relative toxicity of the two preparations is in reverse order to their relative hypotonicity as the preservation-free preparation is more hypotonic than the preparation with preservatives. Thus the pH and osmolarity changes induced by sodium metabisulphite and disodium edetate can be ruled out as causes of the increased toxicity observed with these substances in this study.

Ocular surface toxicity of various preservatives is well known. Wilson, in a wide ranging study, found significant association of benzalkonium chloride, boric acid, chlorobutanol, edetate, parabens, phenylmercuric nitrate, sodium metabisulphite, and thiomersal with the development of adverse drug reactions after topical ophthalmic therapy.[13]

The two preservatives present in the preparation used in group B patients, sodium metabisulphite and disodium edetate, are used as antioxidant and antioxidant synergist respectively. Sodium metabisulphite is known to cause allergic reactions including anaphylaxis particularly in asthmatics.[14] Local ocular toxicity of sodium metabisulphite in the form of corneal endothelial cell breakdown leading to corneal oedema has been demonstrated after the intracameral use of adrenaline containing 0·1% sodium metabisulphite in rabbits and monkeys.[15] Disodium edetate, a chelating agent, has been shown to cause local[16] as well as systemic[17] hypocalcaemia. Wilson identified disodium edetate as the most common preservative to be blamed for contact allergy in ocular drug reactions.[13]

The choice of antibiotic for prophylaxis in cataract surgery is dependent on the microbial spectrum and its adverse effects. The wide microbial spectrum and reduced toxicity achieved by the use of a preservative-free preparation makes gentamicin an appropriate choice in the prophylaxis of ocular infection after intraocular surgery.

Conclusion

The preservatives sodium metabisulphite and disodium edetate cause an increase in the frequency and severity of conjunctival toxicity due to subconjunctival gentamicin injection. We therefore recommend the use of preservative-free subconjunctival gentamicin injection for the prophylaxis of ocular infections following intraocular surgery.

We thank Mrs U K Goddard, Mr A K Mathur, Mr S K Datta and Mr J R Innes for their encouragement and permission to use their patients in this study.

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British Journal of Ophthalmology, 1992, 76, 238–240

Cataract surgery in Fuchs' heterochromic iridocyclitis

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Abstract

Eighteen eyes in 17 patients with Fuchs' heterochromic iridocyclitis underwent cataract extraction with or without intraocular lens implantation (17 extracapsular and one intracapsular). Intraoperative complications included hyphaema, poor pupillary dilatations, and localised zonule dehiscence with vitreous loss. Only four eyes developed a marked anterior uveitus (two pseudophakic and two aphakic) which resolved within 2 weeks with topical steroids. Three eyes developed a rise in intraocular pressure (IOP) to more than 30 mm Hg on the first postoperative day. In all three eyes the IOP returned to normal off all therapy within 1 week. In one of three eyes preoperative glaucoma was made worse following surgery. Visual acuity testing revealed that 15 eyes (83·3%) achieved 6/12 vision or better. Lamellar macular hole, pre-existing macular scar, and pre-existing retinal detachment accounted for the poor visual result.

Fuchs' heterochromic iridocyclitis (FHIC) was first clearly defined by Ernest Fuchs in 1906.[1] This often overlooked uveitis syndrome is characterised by chronic low grade anterior chamber and anterior vitreous inflammation, diffusely distributed stellate keratic precipitates (KPs), full thickness iris atrophy, posterior subcapsular cataract, and abnormal iris blood vessels.[2] FHIC is usually unilateral[3] and progressive iris stromal atrophy leads to heterochromia in most patients. The visual outcome following cataract surgery in patients with FHIC has been the subject of several conflicting reports.[4-9] Until recently little information about visual outcome, complications during surgery, and the role of posterior chamber intraocular lens (IOL) implantation following extracapsular cataract extraction (ECCE) has been available.[10 11] We present the findings of a study on patients with FHIC undergoing cataract extraction with or without IOL implantation.

Patients and methods

All patients with FHIC undergoing cataract surgery at Leicester Royal Infirmary between March 1988 and January 1990 were included in the study. Eighteen eyes of 17 patients were examined preoperatively and the diagnosis of FHIC made according to the presence of standard accepted major and minor criteria.[3 12 13] A record of preoperative use of glaucoma medication and systemic steroids was made and the intraocular pressure (IOP) measured.

Surgery was performed on the 18 eyes by six different surgeons. Twelve eyes were operated on by one of the authors (DRS), and in these patients a particular note was made of complications during surgery including: anterior chamber haemorrhage, poor pupillary dilatation and zonule dehiscence, or posterior capsule tears. Eleven women and six men with ages ranging from 22–77 years underwent surgery. One female patient had bilateral cataract extractions and two patients had previously had cataract extraction on the other eye. Three eyes were being treated for glaucoma with topical medications preoperatively. Seventeen eyes had ECCE and one eye with a subluxed lens had an intracapsular cataract extraction (ICCE) and anterior chamber IOL implanted. Of the 17 eyes having ECCE, five were implanted with posterior chamber IOLs. The decision to implant an IOL was made preoperatively by the surgeon after discussion with the patient. In all patients an aqueous sample was aspirated before anterior capsulotomy and a peripheral iridectomy performed. Betamethasone (2 mg) and gentamicin base (20 mg) were administered subconjunctivally at completion of the surgical procedure. Three patients received preoperative systemic steroids which was continued for 2 weeks following surgery.

After the surgery all patients were treated with hourly topical steroids, topical antibiotics four times daily, and cycloplegics twice daily. All patients were examined postoperatively. Visual acuity was measured with the patients wearing spectacle or contact lens correction. Patients were asked whether they were wearing their contact lens regularly if unilaterally aphakic. The necessity for YAG laser capsulotomy was noted as was any vitreous or retinal pathology. Follow-up ranged from 3 months to 24 months with an average follow-up of 13 months.

PERIOPERATIVE COMPLICATIONS

All 12 eyes operated on by DRS had ECCE. One of these eyes was implanted with a one-piece poly(methylmethacrylate) (PMMA) posterior chamber IOL. Haemorrhage arising from the peripheral iris was noted in all 12 eyes at the time of paracentesis. The blood partially obscured the capsule during capsulotomy in five eyes but was cleared from the central anterior chamber with the use of sodium hyaluronate. Poor pupillary dilatation was noted in four eyes all of which were noted preoperatively to have marked iris stromal atrophy. Localised zonule dehiscence with vitreous loss occurred in one eye.

POSTOPERATIVE COMPLICATIONS

Postoperative hyphaema was not seen in any eye. Four of the 18 eyes developed a marked anterior

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Accepted for publication
6 September 1991

uveitis despite hourly topical steroids. Two of these eyes had been implanted with a posterior chamber IOL and two were aphakic. The uveitis resolved over 1–2 weeks without requiring periocular steroid injection or systemic steroids. None of the three patients receiving preoperative systemic steroids developed significant uveitis. Three eyes developed a rise in IOP to more than 30 mm Hg on the first postoperative day. One of the eyes was already being treated for glaucoma. In all three eyes the IOP returned to normal within 1 week and only required short term treatment with oral acetazolamide. One eye with well controlled glaucoma preoperatively had a rise in IOP 3 weeks postoperatively and has required increased treatment since then (follow-up 14 months). All IOLs were noted to have some KPs on the surface but these were not considered to interfere with visual acuity. Seven eyes were noted to have stellate KPs on the posterior capsule. Three eyes subsequently required YAG laser capsulotomy, two of which were aphakic and one pseudophakic with a posterior chamber IOL.

VISUAL OUTCOME

The visual outcome is given in Table 1.

Fifteen eyes (83·3%) achieved 6/12 vision or better. Three eyes had vision worse than 6/12. Of these one eye was found during surgery to have a pre-existing subtotal rhegamatogenous retinal detachment which was later reattached by vitrectomy and silicone oil but visual acuity remained at hand movements at 0·5 metre. One eye with visual acuity of 6/18 was found to have a lamellar macular hole and one eye with visual acuity of 6/60 had dense vitreous opacities and had a known macular scar preoperatively. Vitreous opacities were noted in all eyes postoperatively but were least apparent in the three eyes with 6/6 or better visual acuity.

CONTACT LENS WEAR

Eight patients were unilaterally aphakic and six of these patients had visual acuity of 6/12 or better with a corrective contact lens. Only two of these patients were regularly wearing their contact lenses.

Discussion

Decisions regarding cataract surgery in patients with FHIC are often influenced by the relatively young age of the patients, the poor experience with cataract surgery in other forms of uveitis, and the tendency of the disease to be unilateral. However the condition may be bilateral as one patient in this series who had bilateral FHIC underwent cataract surgery. The occurrence of the condition binocularly has been reported before. In fact three of the 38 original cases described by Fuchs had slight inflammatory changes in the normal darker eye.[1] More recently in a series of 54 Caucasian patients four (7%) had bilateral involvement.[12]

Table 1 Best corrected operative visual acuity following cataract extraction in 18 eyes with Fuchs' heterochromic iridocyclitis

Snellen acuity	*Pseudophakic eyes*	*Aphakic eyes*	*Total*	*Total cumulative %*
6/5–6/6	2	1	3	16·6
6/6–6/9	1	6	7	55·5
6/9–6/12	2	3	5	83·3
6/12–6/24	1	–	1	89·0
6/24 or worse	–	2	2	100·0

Ward and Hart[6] suggested that there was a high incidence of hyphaema, vitreous haemorrhage, and glaucoma following ICCE in patients with FHIC. More recently Smith and O'Connor[7] in a retrospective review of 29 cases found cataract extraction in FHIC to be only 'slightly more hazardous' than in routine cases. The use of IOLs in FHIC has been given support by Mooney and O'Connor[4] and by Mills and Rosen[5] who found few problems associated with iris fixated IOLs following both ICCE and ECCE. Likewise Gee and Tabbara[10] have recently reported on a series of 15 patients with ECCE with no major intraoperative or postoperative complications. Ten of these patients had capsular fixated posterior chamber IOL lens implantation. In all 15 patients postoperative visual acuity was 6/12 or better.

Jones[11] recently reported his findings from a series of patients with FHIC having ECCE with or without posterior chamber IOLs. He found that anterior chamber haemorrhage was common during surgery, that significant uveitis was present in 25% of patients with IOLs but absent in patients without IOLs, and that a rise in IOP occurred in 33% of eyes. Vitreous opacities were frequently present but visual acuity was 6/12 or better in 70% of eyes with IOLs and 80% of eyes corrected with contact lenses. We have found haemorrhage following paracentesis to be invariable in FHIC. This haemorrhage appears to be caused by lowering the IOP, and the effects may be minimised by the use of sodium hyaluronate before performing anterior capsulotomy. We observed no postoperative hyphaema. This may have been due to effective wound closure avoiding postoperative hypotony. Postoperative uveitis occurred in four eyes (22%) but unlike Jones[11] we did not find any association with IOL use.

Preoperative treatment with systemic steroids may reduce postoperative uveitis as has been suggested in other uveitis syndromes.[14] This was the case in three patients in this study. Although four eyes had raised IOP postoperatively only one eye has shown a sustained rise requiring more treatment than was needed before the surgery. The visual outcome in our series is similar to that of Jones' series[11] but slightly worse than in Gee's series.[10] Though the number of patients achieving 6/12 or better is high one would expect a higher number of 6/6 or better eyes in these relatively young patients. This slight reduction in visual acuity appears to be caused by vitreous opacification which is known to be as common in FHIC as cataract itself. None of our patients has had vitrectomy for vitreous opacities but cataract surgery combined with vitrectomy for vitreous opacities may lead to a better visual result. Stellate KPs on both the IOLs and the posterior capsule were common but were not considered when making the decision whether to implant an IOL or not.

Conclusion

Cataract extraction in patients with FHIC is only slightly more difficult than in patients with senile cataract. Efforts should be made to minimise postoperative uveitis by preoperative treatment with steroids systemically or locally. Visual outcome is often slightly compromised due to persistent vitreous opacities. IOL implantation in this series does not appear to be associated with increased risk and in view of the poor compliance with contact lens wear should be considered in the patient with unilateral FHIC.

This study was supported in part by the Anne Allerton Fund.

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British Journal of Ophthalmology, 1992, **76**, 241–243

Low dose cyclosporin A versus pulsed cyclophosphamide in Behçet's syndrome: a single masked trial

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Accepted for publication 20 September 1991

Abstract

A single masked trial of cyclosporin A 5 mg/kg/day versus monthly 1 g intravenous boluses of cyclophosphamide was conducted among 23 patients with Behçet's syndrome and active, potentially reversible uveitis. The trial was unmasked after a mean of 12 (SD 2) months for the cyclosporin A group ($n=12$) and a mean of 10 (SD 3) months for the cyclophosphamide group ($n=11$). During the initial 6 months the visual acuity significantly improved ($p<0{\cdot}001$) in the cyclosporin A group whereas this was not observed in the cyclophosphamide group. The subsequent follow-up of patients up to 24 months suggested that the initial improvement in visual acuity with cyclosporin A was not sustained. More extensive and especially long-term studies of cyclosporin A in the uveitis of Behçet's syndrome are warranted.

Eye involvement occurs in approximately half of the patients with Behçet's syndrome and may also lead to blindness in around one fifth.[1] Recently many open trials[2-12] and one masked trial[13] of cyclosporin A reported favourable results in treating eye disease in Behçet's syndrome. However the dose of cyclosporin A used in these studies was high (6–10 mg/kg/day) according to the recent understanding of the toxicity of this drug.[14,15] Furthermore in some of these studies patients with non-Behçet's uveitis (that is, endogenous uveitis, Vogt-Koyanaga Harada syndrome) were included.[3,7,11,12] This makes the interpretation of the results of these trials difficult. Here we report a pilot, controlled, and single masked trial of low dose (5 mg/kg/day) cyclosporin A versus cyclophosphamide (1000 mg intravenous bolus/month) in 23 Behçet's patients with severe eye involvement. The trial was unmasked 7 months after the entry of the last patient due to the observed and reported[16] efficacy of cyclosporin A in treating Behçet's syndrome. The subsequent follow-up of the trial patients using cyclosporin A up to 24 months is also reported.

Patients and methods

Twenty three Behçet's patients with active potentially reversible eye disease were studied at Behçet's Syndrome Outpatient Clinic at Cerrahpaşa Medical Faculty. The make-up of this clinic is described in detail elsewhere.[1] All patients had bilateral severe uveitis with mainly posterior involvement and at least three ocular disease exacerbations (attacks) within the preceding 6 months. Patients who had end stage disease, with mainly irreversible retinal damage and blindness preventing their evaluation, were excluded. All patients fulfilled the recently reported international diagnostic criteria.[17]

At the beginning of the trial the patients were assigned alternatively to receive either cyclosporin A solution 5 mg/kg/day or monthly intravenous boluses of 1000 mg of cyclophosphamide after an explanation of the investigative nature of the study and obtaining their consent. However they were free to choose either treatment modality irrespective of their initial allocation. The mean weight of the patients to receive cyclosporin A was 66·4 (SD 10·4) kg and the mean weight of those to receive cyclophosphamide was 64·0 (SD 9·7) kg.

Cyclosporin A solution was given by mouth in two divided doses. All patients were required to attend the clinic once a week during the first month and monthly thereafter. Measurements of body weight, pulse rate, blood pressure, serum creatinine, and serum cyclosporin A levels were performed at each visit and total blood counts, liver function tests (ALT, AST, bilirubin, and alkaline phosphatase), and urinalyses every 3 months. Each month 1000 mg doses of cyclophosphamide were given intravenously in 1 litre of 5% dextrose solution over 1 hour. Total blood and platelet counts were done on each visit before pulsed cyclophosphamide therapy.

A full ophthalmological evaluation was performed by the same observer (YÖ) who was initially masked to the outcome of drug allocation. Special attention was given to visual acuity and the occurrence of eye attacks. The visual acuity in evaluating the results was expressed by taking the mean of the numerators for each eye on a 0–10 Snellen chart. A new attack was defined as an increase or development of inflammatory cells in anterior chamber, flare, vitreous haze, all graded on a 0–4+scale. Furthermore, the mere presence or absence of retinal vasculitis, macular oedema, vascular sheathing, venous occlusion, and vitreous condensation were also recorded at each visit. Of these parameters the emergence of macular oedema or of retinal vasculitis was also interpreted as an indicator of a new attack. Dermatological evaluation was graded as 'worse' (−1), 'same' (0), 'better' (+1), both by the patient and the dermatologist (again single masked). An internist (SY) ran the study as the primary care physician and made the necessary dose adjustments. No patient had been taking immunosuppressive drugs during the preceding 6 months of entry to the trial. However there were three patients taking steroids.

One patient was in the cyclosporin A group taking prednisolone 20 mg every other day and two were in the cyclophosphamide group, one using 10 mg and the other 5 mg/day of prednisolone.

The study was initially planned to last 24 months. Seventeen months from the entry of the first and 7 months after the last patient the trial was unmasked due to the apparent beneficial affects of cyclosporin A observed by the non-masked members of the study group and similar reports of investigators from other centres.[16] However during the open phase the formal monthly evaluations of the patients were carried out up to 24 months.

Results

Table 1 shows the demographic characteristics, the disease duration, and severity of eye disease at the time of entry into the trial. All patients had bilateral eye disease. It was noted that all 12 patients using cyclosporin A were males as the females refused to use cyclosporin A because of risk of potential hirsutism. There were however six males and five females in the cyclophosphamide group. The mean age at entry, duration of eye disease, and the mean visual acuity were similar between the two groups. There were no statistically significant differences in the scores of inflammatory cells and flare in the anterior chamber and vitreous haze between the two groups at the onset of the trial.

The trial was unmasked after a mean of 12·30 (SD 2·36) months for the patients in the cyclosporin A group and 9·80 (SD 3·42) months for those in the cyclophosphamide group (t=1·90, 0·10>p>0·05). During this time two patients from the cyclosporin A group were lost from the trial. One was at month 9 when he developed hepatitis B and had to be withdrawn. The second one was a no-show after 3 months. During the same time there was one loss at month 11 from the cyclophosphamide group for unknown reasons. After the trial was unmasked there were two further losses from the cyclosporin A group at months 11 and 21, again without apparent causes.

Table 1 Patient characteristics

	Number	Male/ female	Age at entry (years)	Duration of eye disease (years)	Mean visual acuity at entry
Cyclosporin A	12	12/0	29 (6)* (15–39)†	2·64 (1·58) (1–5·5)	4·46 (2·96)
Cyclophosphamide	11	6/5	32 (6) (25–41)	2·39 (2·37) (0·5–8)	4·77 (2·65)

*SD in parenthesis.
†Range.

Table 2 Visual acuity

	At entry	At 6 months	At the time of unmasking of the trial*	At 24 months
Cyclosporin A	4·46 (2·96)† (*n*=12)	6·82 (2·98)‡ (*n*=11)	4·75 (4·84) (*n*=10)	4·50 (2·94) (*n*=8)
Cyclophosphamide	4·77 (2·65) (*n*=11)	4·14 (3·09) (*n*=11)	3·95 (2·30) (*n*=10)	not comparable

*See text for duration of the masked periods for each group.
†SD in parenthesis.
‡t=5·47, p<0·001 versus visual acuity at entry (paired t test).

Table 3 Number of ocular attacks per patient per month

	Up to 6 months	From 6 months to the time of unmasking of the trial	From the time of unmasking of the trial to 24 months
Cyclosporin A	0·48 (0·28)*† (*n*=11)	0·49 (0·52) (*n*=10)	0·51 (0·46) (*n*=8)
Cyclophosphamide	0·62 (0·22)† (*n*=11)	0·60 (0·51) (*n*=10)	not comparable

*SD in parenthesis.
†t=1·30, p>0·02.

Only four patients from the cyclophosphamide group completed the 24 months continuing to use bolus cyclophosphamide. Of the remaining six patients four were switched to cyclosporin A, one to oral cyclophosphamide, and one to weekly doses of methotrexate.

The mean dose of cyclosporin A which could be used was 4·89 (SD 0·54) mg/kg/day during the first 6 months of the masked period and 4·49 (SD 0·94) mg/kg/day during the rest of the trial (t=1·60, p>0·10). The mean plasma level of cyclosporin A was 131·20 (SD 13·80) ng/ml during the masked phase. Plasma levels were not routinely done during the open phase. Among the eight patients who completed the full 24 months using cyclosporin the mean serum creatinine level at the time of entry was 70 (SD 7·01) μmol/litre and 79 (SD 17) μmol/litre at their last visit (t=2·02, 0·10>p>0·05). No patient had to be withdrawn due to any form of drug toxicity.

The alternate day steroid that was being used in one patient in the cyclosporin A group was gradually tapered down and was stopped at 9 months. This was the same patient that had to be withdrawn because of hepatitis B. The steroid use in two patients in the cyclophosphamide group was stopped after the first month.

Table 2 depicts the mean visual acuity at four different points in the trial and shows that visual acuity significantly improved when compared with that observed at entry in the cyclosporin A group at 6 months (p<0·001). This initial improvement however had disappeared by the time the trial was unmasked. The visual acuity among the eight patients continuing to use cyclosporin A at the end of 24 months remained approximately the same as that at the time of unmasking the trial or as that at entry. No statistically significant change in visual acuity among the patients using cyclophosphamide occurred at the three time points, apart from a trend to deterioration at the time of unmasking the trial when compared with that at the time of entry.

As seen in Table 3 although there was a trend for fewer ocular attacks in the cyclosporin A group this did not assume statistical significance for the time intervals assessed.

Statistical analysis of other pathology related to the eye (retinal vasculitis, macular oedema, etc.) was not attempted because of few events in a small number of patients. Although the effect of cyclosporin A and cyclophosphamide on the extraocular manifestations of the disease were also recorded again there were too few events in our small group of patients to perform a formal analysis.

Discussion

During the initial 6 months the most relevant outcome of eye involvement, the visual acuity, fared significantly better among the cyclosporin

A users compared with those using cyclophosphamide. Even though only a small number of patients could be studied it was possible to demonstrate this effect. The 6 month interval was arbitrarily chosen as a convenient time span when the effect of the two medications could be compared between the maximum number of patients from each group. Furthermore in the allocation of patients to the treatment groups there was a definite bias towards females among the cyclophosphamide users. This was mainly due to patient refusal of cyclosporin A because of risk of potential hirsutism.[14] Behçets syndrome runs a more severe course in the male and this is also true for eye disease.[1] Thus the more beneficial effect of cyclosporin A compared with cyclophosphamide would perhaps have been more apparent had there been a more even sex distribution of the patients.

The long term effect of cyclosporin A on visual acuity as observed in this study was somewhat disheartening especially in the light of the favourable effect noted during the early phase. It can be said that the visual acuity during the open phase cannot legitimately be compared with that in the masked phase because of possible observer bias. However as noted in Table 2 the trend for dampening of the beneficial effect of cyclosporin A begins before the time when the code is revealed. On the other hand the preservation of the mean visual acuity among the eight patients who completed the full 24 months can be taken as a clue to the efficacy of cyclosporin A in the treatment of eye disease in Behçet's syndrome. In a placebo controlled study of azathioprine recently reported by our group[18] the mean visual acuity had significantly deteriorated among the placebo users after 24 months. It is to be noted that in the azathioprine study[18] the patients had not been specifically selected for active eye disease as was the case in the current study.

We believe that cyclosporin A is a useful and, currently, perhaps the most effective agent for the treatment of eye disease in Behçet's syndrome. This seems especially true for its short term use. Its potential usefulness over longer periods however needs to be further elucidated by carefully conducted studies in greater number of patients using acceptable doses.

We thank the Sandoz company for their supply of cyclosporin A (Sandimmun) and Mrs Emine Öztürk for her secretarial assistance.

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British Journal of Ophthalmology, 1992, 76, 244–245

MINI REVIEW

Ophthalmic zoster

Ophthalmic herpes zoster is a disease varying in severity from devastating, threatening life and sight, to so mild that it may pass unnoticed. The ophthalmic division of V is involved in 7–17·5% of all herpes zoster patients, affecting many of the tissues of the globe and orbit by highly varied types of lesions.

The current theory of aetiology is that after an attack of chickenpox and its attendant viraemia some virus is retained in the dorsal root ganglion, perhaps reaching there by retrograde spread along the sensory nerves from the skin lesions. Later, under the influence of largely unknown trigger factors it reactivates replicates and migrates back down the sensory nerves to the skin and eye where it causes its characteristic lesions. Virus has been cultured from these sites in the acute stage of the disease.

Varicella zoster virus (VZV) or as it is now known human herpes virus 3 (HHV3) is a typical herpes virus containing DNA, an icosahedral nucleocapsid, and a glycoprotein containing outer cell membrane. It is indistinguishable by electron microscopy from other members of the herpes family. Recently several different strains of virus have been identified by means of restriction endonuclease analysis.[1] However, overall, scientific research into the virus has been sketchy due to difficulties in obtaining cell-free virus, in culturing it, and failure to find a satisfactory animal model.

Reactivation of latent virus is often stated to be associated with a temporary depression of immunity and there have been many studies attempting to confirm this. So far there is no information immediately prior to developing the disease. However, shortly after onset, there is a clear anamnestic rise in circulating antibody demonstrating that the virus has been encountered before and there is a consistent depression of cell-mediated immunity (this may be an artefact due to recruitment of immunologically competent cells into the affected tissues). There is also a reversal of T cell subsets[2]: the number of cytotoxic lymphocytes increases and these have the capacity to destroy the virus. Interestingly the disease is no worse in those with defects in circulating immunity but is undoubtedly more common and severe in those with established impairment of cell-mediated immunity such as AIDS and Hodgkin's disease. Nevertheless the vast majority of ophthalmologists' patients are previously healthy and the mechanism of reactivation remains unknown.

Epidemiology shows that there is no seasonal incidence but there is a steady increase in incidence with age. Second attacks occur in about 4% of patients.

Pathologically virus has been identified in the trigeminal ganglion very early on[3] and is accompanied by a perineuritis and perivasculitis which lead to varying degrees of neuronal necrosis and fibrosis. The adjacent brain stem and carotid artery may be involved by the inflammatory process and encephalitis, isolated cranial palsies, and late hemiplegia may ensue. Severe skin lesions are characterised by haemorrhagic bullae probably caused by a dermal vasculitis. This too is followed by extensive necrosis and scarring. The globe shows marked cellular infiltration in the neurovascular bundles and frequently a perivasculitis in iris and ciliary body. Damage to the ocular tissues may be direct, as the result of the cellular infiltration, or indirect by denervation and the ischaemia induced by the vasculitis. These changes may be chronic and relapsing but in spite of it being assumed that they are due to continuing virus replication there is no scientific evidence barring the recent discovery of viral DNA in old enucleated eyes and corneal buttons.[4]

The disease can be divided into three phases: an acute phase (within the first 4 weeks) which may totally resolve, a chronic phase (which may persist for years) and a relapsing phase where the acute or chronic lesions appear to have been controlled but break through again (even years later).

The commonest ocular lesions are conjunctivitis, punctate epithelial keratitis, episcleritis, iritis, and nummular keratitis, of which the first two are very transient and resolve quite rapidly without treatment. Many cases of episcleritis are indolent and seem to respond best to oral Froben (flurbiprofen) which is easily withdrawn. Nummular keratitis has a very variable course; some cases resolve without trace after a minimum of treatment, others become indolent with chronic cellular and lipid infiltration accompanied by faceting which may seriously interfere with vision. Unfortunately this tends to occur more in young people and therefore these lesions should be observed carefully and treated with low doses of topical steroid when active. Acute lesions giving rise to problems in management are hypertensive iritis, acute corneal oedema, disciform keratitis, sclerokeratitis, and neurotrophic ulcer. Both systemic and topical acyclovir (ACV) seem to have little effect on them and invariably potent topical steroids have to be used in all but the corneal ulcers. The disadvantage of this is the dependency on steroids that develops and the difficulty in weaning patients off the drug: it can take years. Chronic lesions which are troublesome are neurotrophic, mucous plaque (MPK), exposure and lipid keratitis. The first is best treated with taping the lids closed, botulinus toxin-induced ptosis, or a partial tarsorrhaphy. All too often a severe central scar ensues that is very unfavourable to keratoplasty. MPK has a tendency to recurrence, particularly in association with a glaucoma that is difficult to manage medically, but responds well to surgery. It may go onto a neurotrophic or exposure keratitis. Exposure keratitis is very difficult to manage; artificial tears and lid toilet are often disappointing. It may be necessary to carry out a tarsorrhaphy and a superficial keratectomy. Lipid keratopathy can be prevented by adequate suppression of inflammation but, if established and with good corneal sensitivity, does well with keratoplasty. All these lesions respond poorly to systemic and topical ACV.

Systemic treatment of zoster patients is controversial and largely ineffective. Steroid and ACV have been advocated in the very early stages.[5,6] I feel the former should be used in immunocompetent patients with optic neuritis, haemorrhagic skin bullae, total external ophthalmoplegia with proptosis, and contralateral hemiplegias by means of a pulsed dose of 80 mg of prednisolone rapidly reduced over 1 week. ACV, on the other hand, should be used in the immunosuppressed but has a doubtful effectiveness in the immunocompetent with regard to the prevention of post-herpetic neuralgia and development of ocular complications.[7,8]

A significant degree of post-herpetic neuralgia (PHN), defined as pain after the first 6 weeks, occurs in about 7% of patients and is notoriously difficult to treat. The list of cures is legion; presently fashionable are stellate ganglion block, cimetidine, transcutaneous electric nerve stimulation

(TENS), and acupuncture. It is probably best to try to treat the acute neuralgia fully with analgesics as there is some evidence that this may reduce the degree of PHN. There may be a severe accompanying depression compounding the problem and this responds well to amitriptyline.

Perhaps the most misleading complications are the recurrent lesions which may present years after the original disease. Therefore meticulous follow-up is needed in all complicated zoster. We are still very ignorant of the pathogenesis of the disease and the part, if any, the virus plays in chronic and relapsing lesions. The search must continue for a more effective antiviral drug but if viral replication is confined to the onset of the disease and if the later lesions are, as seems likely, due to immunologically mediated reactions not dependent on the presence of live virus (as we know it), the results will not prove useful unless the antiviral drug is administered at the very onset of the disease. Thus anti-inflammatories, mainly in the form of topical steroids, remain the backbone of treatment for the severe ocular complications of zoster.

R J MARSH

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British Journal of Ophthalmology, 1992, 76, 246–247

CASE REPORTS

Lid melanoma and parkinsonism

S A Haider, V T Thaller

Abstract

This is a case report of a patient with parkinsonism on levodopa therapy who developed a lid margin melanoma. The possible association is discussed.

Case report

A 73-year-old Caucasian woman was referred because of raised intraocular pressures. She was more concerned by an enlarging pigmented lid margin lesion which had been present for 5 years.

The patient had been treated for parkinsonism. At the time of presentation she was being treated with: Sinemet (carbidopa 10 mg+levodopa 100 mg)×6 since 1979, ophenadine 300 mg, Selegiline 5 mg twice daily, quinine sulphate 200 mg at night, piroxicam 10 mg twice daily, and temazepam 20 mg at night.

Examination revealed a pigmented slightly raised skin lesion on the left lower lid measuring 10 mm×5 mm (Fig 1). It was darkly pigmented with less pigmented edges. There was no regional lymphadenopathy.

A full thickness lid excision biopsy with 2 mm clear margins was performed and the defect repaired by direct closure (Fig 2).

Histology (Fig 3) revealed a superficial spreading malignant melanoma. Most of it was still in situ but in one area there was invasion of upper dermis (level 2) with a Breslow thickness of 0·3 mm. The biopsy margins were tumour free.

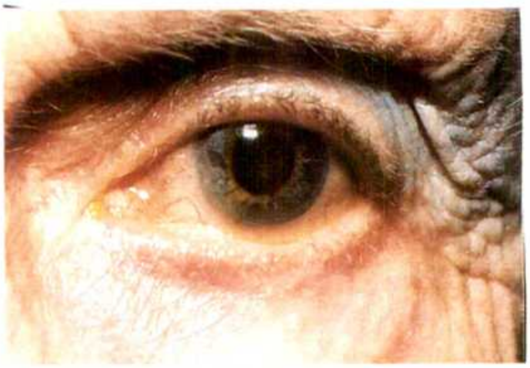

Figure 2 Three months postoperative appearance following 14 mm horizontal full thickness lid excision and primary direct closure of the defect.

Discussion

Levodopa has been in extensive use for parkinsonism since the 1960s. Skibba[1] first reported a case of malignant melanoma arising in a patient on levodopa and raised the possibility of a causal relationship between levodopa and malignant melanoma. This was followed by sporadic reports[2 3 4 5 6] of melanoma arising de novo or in pre-existing naevi in patients on long term levodopa therapy. Rampen[7] reported three new cases and reviewed from 16 cases already present in the literature.

This is another report of a patient developing malignant melanoma while on long term levodopa therapy.

Melanocytes have the specialised tyrosinase enzyme system that converts levodopa into melanin. Wick *et al*[8] showed that in the presence of dopa decarboxylase inhibitor, levodopa, is selectively incorporated into melanocytes. This raised the possibility of levodopa being a carcinogen for melanocytes. Rampen has argued against this saying that the presence of excess of substrate probably leads to enhancement of the

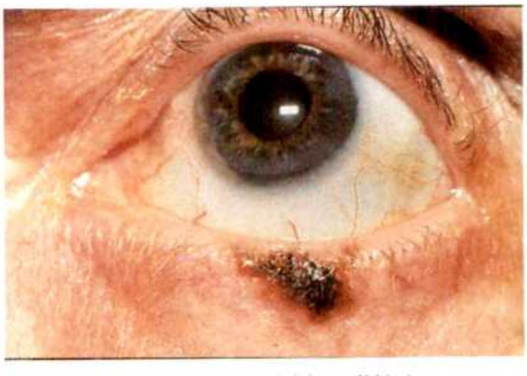

Figure 1 Pigmented enlarging left lower lid lesion.

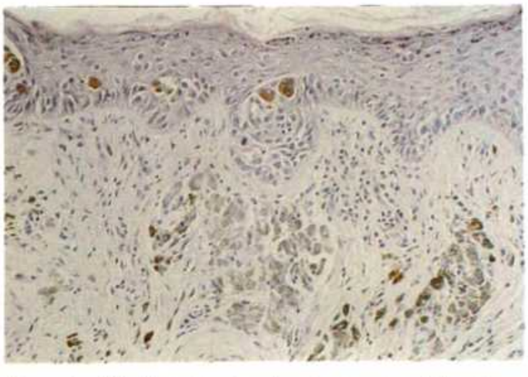

Figure 3 Histological section showing invasion of the upper dermis by melanoma cells (pigmented brown) (H & E ×60 magnification).

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Accepted for publication
1 August 1991

enzyme systems related to melanin synthesis, that is cell differentiation. This may reduce the reproductive rate and hence the malignant potential of melanocytes.

Wick *et al* have demonstrated that levodopa may be toxic to melanoma cells. This however does not exclude levodopa from being a carcinogen since long term exposure to cytotoxic agents may in itself increase the risk of neoplasm development.

However a carcinogenic role for levodopa remains questionable because of the scarcity of reported cases. Sober and Wick[10] in their prospective study of 1099 cutaneous melanoma patients found only one patient who was on levodopa.

In conclusion the link between levodopa and melanoma remains tenuous but because the possibility has been raised there remains a need for vigilance.

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British Journal of Ophthalmology, 1992, **76**, 248–249

Capsular 'pits' in the human lens

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Accepted for publication
13 September 1991

Abstract

The lens capsule is an atypical basement membrane surrounding the lens epithelial cells and lens fibres which make up the remainder of the human lens. A seemingly unreported morphological change visible in the lens capsule with the biomicroscope is described.

The clinical appearances are of multiple small cystic lesions in the central area of the anterior lens capsule. These are mostly circular and approximately 50 μm in diameter; oval and yeast-like shapes are also seen. The overall effect is very reminiscent of the pebbled glass pattern seen in bleb dystrophy of the corneal epithelium. They are seen most clearly by retro-illumination and exhibit the unreversed effect described by Brown.[2] From this we can conclude that they are areas of lower refractive index than the surrounding capsule. With focal slit illumination the lesions are localised to the lens capsule with minimal distortion of the underlying anterior clear zone of the lens (C1 α). When viewed using specular reflection dark areas are evident, with high well defined margins, an appearance similar to moon craters. From this we conclude that they are most probably pits in the front surface of the capsule.

Case reports

All patients were seen as part of routine toxicity monitoring studies performed at the Clinical Cataract Research Unit, Nuffield Laboratory of Ophthalmology, Oxford.

CASE 1

A 64-year-old woman with a history of coronary thrombosis and systemic hypertension. At the time of examination her medications were: isosorbide dinitrate, atenolol, nifedipine, and simvastatin. Ocular examination was normal except for map-dot dystrophy of the cornea. The capsular abnormalities described above were found in both lenses. The right lens had a few white focal dots, the left lens had grade 1 vacuoles and retro-dots (Oxford grading[3]). There had been no visual symptoms and the visual acuity was right eye −0·14, left eye −0·18 Log Mar (6/5, 6/5+Snellen).[4]

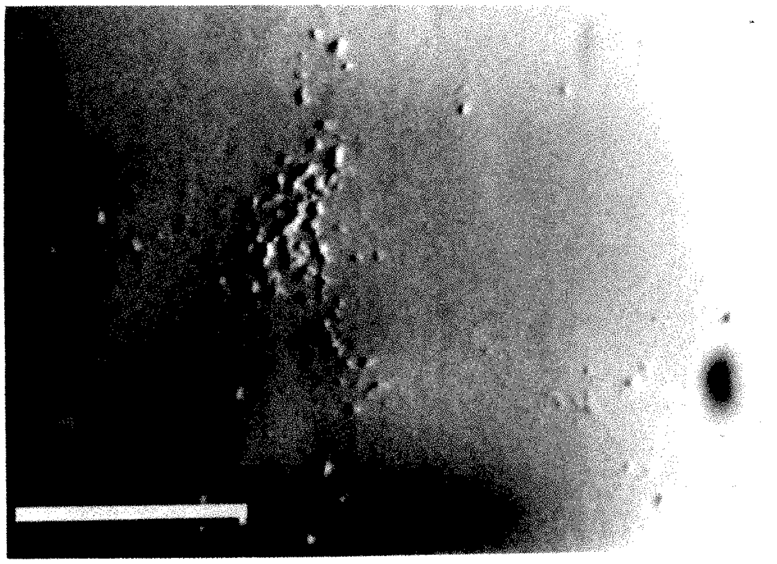

Figure 1 Pits in the lens capsule photographed by retroillumination. Illuminating beam from patient's left (patient 2). Bar=1 mm.

CASE 2

A 51-year-old man with a previous history of myocardial infarction and hypercholesterolaemia. At the time of examination his only medication was simvastatin. The visual acuity was right eye −0·10, left eye −0·14 Log Mar (6/4, 6/4+Snellen); he had no visual complaints. Ocular examination was entirely normal except for the lenses; both had some focal dots and peripheral coronary opacities were noted on the right side (Fig 1). In addition both anterior capsules displayed the abnormalities described above.

CASE 3

A 57-year-old man with a history of myocardial infarction and hypothyroidism. At the time of examination his medication was 1-thyroxine and metoprolol. The corrected visual acuity was right eye −0·08, left eye −0·10 Log Mar (6/5+6/4 Snellen); he had no visual complaints. Ocular examination was normal, with grade 1 focal dots in each lens (Oxford grading). Both lens capsules displayed pit-like changes (Fig 2).

CASE 4

A 49-year-old man with a history of angina pectoris. At the time of examination his medication was atenolol. He had no visual complaints. The visual acuity was −0·10 right eye, −0·10 left Log eye Mar (6/4, 6/4 Snellen). Ocular examination showed bilateral pingeculae. There were grade 1 cortical spoke opacities in the left lens and both eyes had pit-like changes in the anterior lens capsules.

Discussion

The descriptive analysis of the lens by Vogt in his *Atlas of Biomicroscopy* gives detail of the lens capsule. Attention is drawn to the shagreen pattern seen in the mature lens and to variations in this appearance.[5] Latterly this has been used to approximate the size of the lens epithelial cells,[6 7] and we have used these calculations to estimate the magnitude of the pit-like structures which we have observed. Vogt goes on to describe

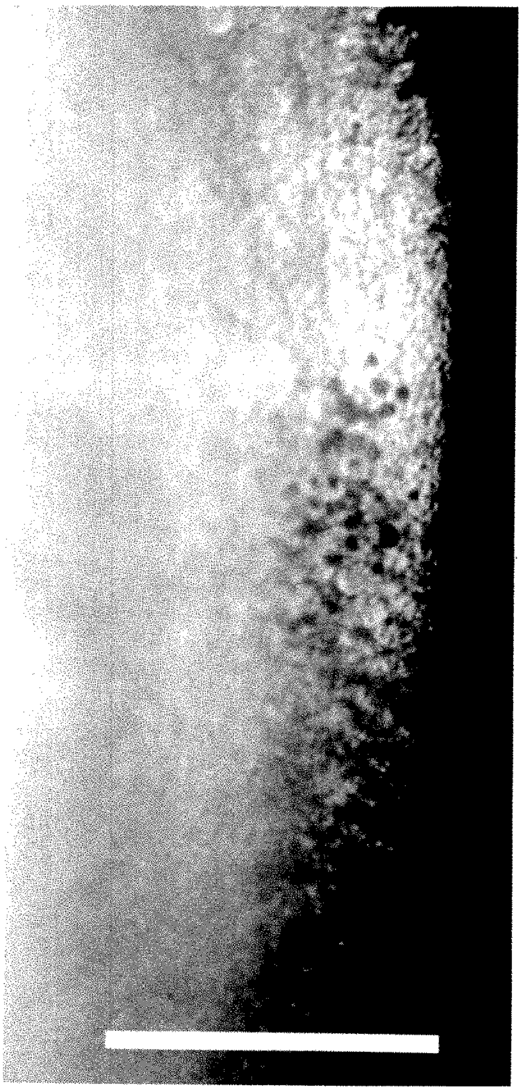

Figure 2 Pits in the lens capsule. Photograph of the specular reflex (patient 3). Bar=1 mm.

wart-like excrescences on the aging lens capsule usually found toward the periphery of the lens, clearly distinct from the current phenomenon. Deposits on the capsule are a frequent finding. Pigmented cells are seen either as an epicapsular star, where they represent remnants of the pupillary membrane or as the result of intraocular inflammation. The dandruff-like accumulation of the pseudoexfoliation syndrome is commonly found with increasing age. Punctate stippling of the lens capsule has been noted in hypocalcaemia along with cataract[8] but there is no previous description of pit-like changes in the healthy lens.

As a group the patients in whom we have seen pit-like change of the capsule all suffer from ischaemic heart disease. It is possible that this is significant, but it may merely reflect the current pattern of toxicity monitoring being undertaken in our research unit.

There is little doubt that the lens capsule is produced by the lens epithelial cells. Biochemically the capsule has the same molecular components as basement membranes elsewhere in the body.[9] The predominant protein is type IV collagen, a triple helix of molecular weight 160 000–180 000. Laminin, entactin, and fibronectin are found throughout the membrane.[10] Many functions have been suggested for these glycoproteins. For example laminin has areas on the short arms of the molecule which bind to type IV collagen, as well as fitting to identifiable receptors on the plasma membrane. Fibronectin is a V-shaped molecule with multiple binding sites and has been described as a cell matrix ligand. The molecular architecture of basement membrane consists of laminin and heparan sulphate proteoglycan (HSPG) embedded within a network of type IV collagen. The turnover of basement membrane appears to be slow, about 100 days in the glomerular basement membrane in the rat.[9] The secretion of basement membranes by epithelial cells appears to be a piecemeal process followed by progressive extracellular self-assembly.[11]

The foregoing biochemical evidence suggests two possible pathological mechanisms for lesions within basement membranes. Firstly, errors in biosynthesis and/or metabolism and, secondly, proteolytic attack. In the eyes which we have reported there has been no evidence of inflammatory change or immunological activity to support the second of these mechanisms. The question then arises as to why errors in biosynthesis and/or metabolism should affect the central area of the capsule. There is a further potential pathological influence upon the lens capsule unique to its position within the ocular media – light damage by a photothermal mechanism. Extreme photothermal damage to the capsule produces true exfoliation of the lens capsule, a recognised occupational hazard in those exposed to infrared radiation such as glassblowers and foundry workers.[12] None of our patients have a history of such exposure. More recently alterations of the anterior lens capsule have been described in association with climatic droplet keratopathy. Frosting of the lens capsule was the first recorded sign followed in more severe cases by plateau formation and in the most severe 'bagging' of the capsule with herniation through the pupil. The severity of the capsular changes was strongly associated with climatic droplet keratopathy, the inference being that the cause was ultraviolet light exposure.[13] It is possible that the pit-like changes under discussion represent a similar though less marked light induced phenomenon in people from a temperate climate.

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British Journal of Ophthalmology, 1992, **76**, 250–251

Bilateral macular coloboma and pigmented paravenous retinochoroidal atrophy

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Accepted for publication 27 September 1991

Abstract

A patient had bilateral macular coloboma with aggregations of pigment clumps located perivascularly, predominantly paravenously, and in other parts of the retina. The *Toxoplasma* IgG antibody was negative. The diagnosis of bilateral macular coloboma with pigmented paravenous retinochoroidal atrophy was made and seemed to be a developmental abnormality in origin.

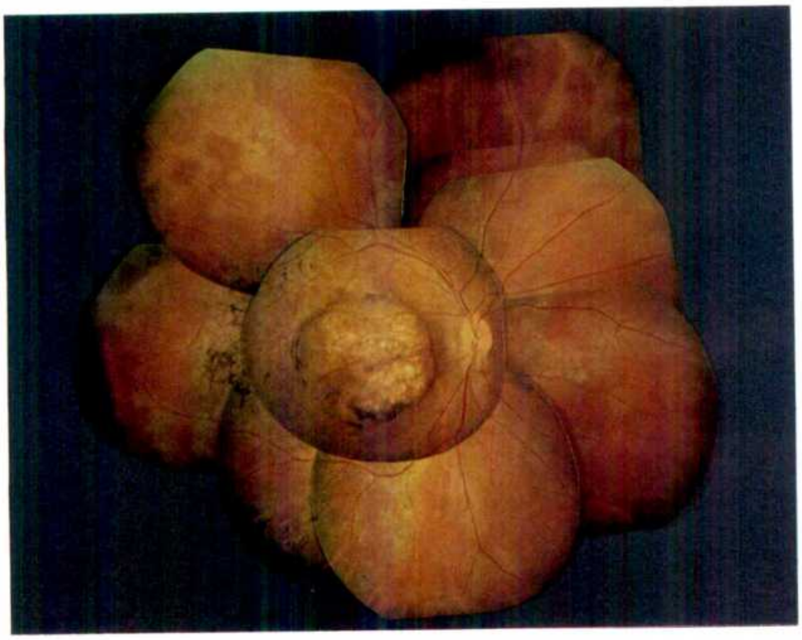

Figure 1 Retinal photograph of right fundus.

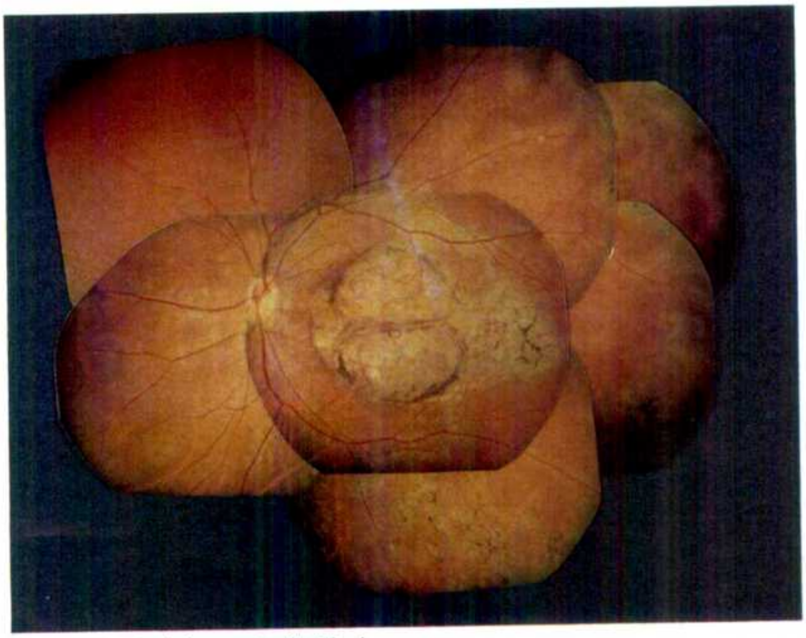

Figure 2 Retinal photograph of left fundus.

Macular coloboma is thought to result from intrauterine inflammation or as an abnormality of development. Most cases are now recognised as being due to an intrauterine infection with *Toxoplasma gondii*. A developmental abnormality seems to be the cause in those patients with a hereditary or family origin,[1,2] and those with other ocular or systemic abnormalities.[3-8]

We report a case of bilateral macular coloboma associated with pigmented paravenous retinochoroidal atrophy and negative *Toxoplasma* IgG antibody in which the macular lesions seem to be of a developmental origin. To our knowledge the appearance of these two congenital anomalies has not been previously reported in the English literature.

Case report

A 23-year-old woman presented with a history of progressive blurring of vision in both eyes for a duration of 8 years. There was no contributory medical or family history.

Examination of the patient revealed the best corrected visual acuity as 20/400 in both eyes. The anterior segments were normal. Ophthalmoscopy showed a bilateral excavated, non-pigmented macular coloboma about 4×4 disc diameter in size with ectatic sclera at the base. A few large choroidal vessels were visible at the base and the retinal vessels crossing the defect were attenuated. The optic discs were normal. Aggregations of pigment clumps were located perivascularly, mainly paravenously, and in some other parts of the retina. Zones of peripapillary and radial patches of chorioretinal atrophy were situated behind the pigmented muffs and mainly along the vessels (Figs 1 and 2). Fluorescein angiography showed hypofluorescence with filling of the choroidal vasculature in both coloboma areas with a rim of hyperfluorescence surrounding the margin in the later phase of the examination. There were also blocked fluorescence from the pigment clumps and the pigment epithelial window defect due to pigment epithelial atrophy (Figs 3 and 4). The Farnsworth-Munsell 100-hue test showed a mild colour vision defect. Goldmann perimetry examination revealed central scotoma with constricted peripheral fields. Electroretinography showed a reduction in b-wave amplitude. Dark adaptation curves showed monophasic and elevated final rod thresholds in both eyes. Ultrasonography showed a bilateral ectatic base with an axial length of 21·8 mm in the right eye and 22·0 mm in the left eye.

A systemic evaluation, including skull and chest *x* rays, complete blood count, erythrocyte sedimentation rate, antinuclear antibody,

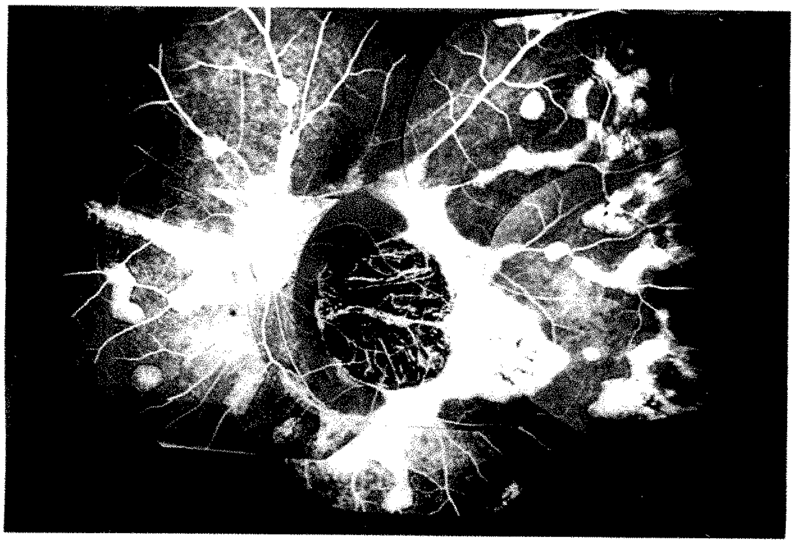

Figure 3 Fluorescein angiography of right fundus.

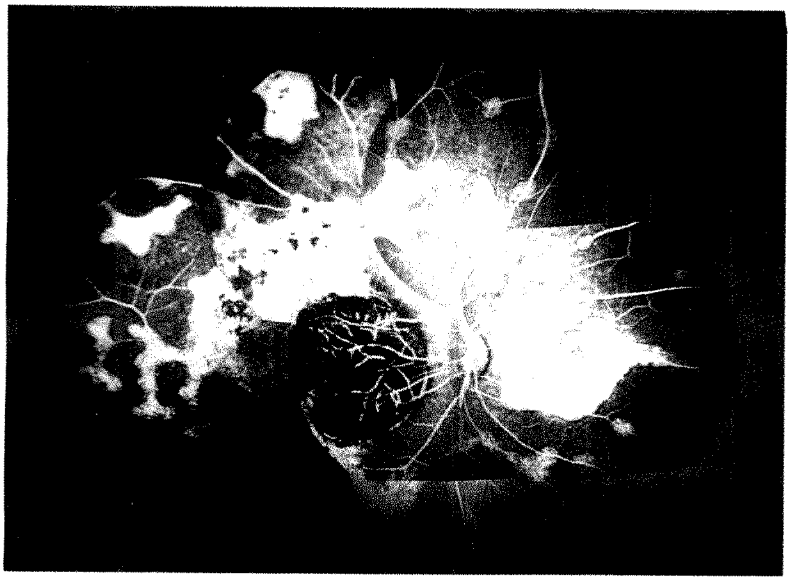

Figure 4 Fluorescein angiography of left fundus.

C-reactive protein, and VDRL test was noncontributory. Serological tests for cytomegalovirus, rubella, and herpes simplex were negative. A *Toxoplasma* IgG antibody test was negative at 1 in 10 dilutions by using an indirect fluorescence test.

Discussion

The patient described herein showed a bilateral macular coloboma and perivascular, mainly paravenous, aggregations of pigment clumps.

Mann[9] classified macular coloboma into three types, namely pigmented macular coloboma, non-pigmented macular coloboma, and macular coloboma associated with abnormal vessels. The present case did not fall clearly into any of these three types. Though the macular lesion seemed to be of the non-pigmented type paravenous pigment aggregations showed a peculiar manifestation.

Macular coloboma is known to develop from an intrauterine inflammation or as a developmental abnormality of the eye. The majority of cases are due to intrauterine *Toxoplasma* infection.[10] However the infective process does not produce macular coloboma in families or in association with other ocular or systemic abnormalities such as retinitis pigmentosa,[3] Leber's amaurosis,[4] retinal dystrophy,[5] idiopathic infantile hypercalciuria,[6] or a specific skeletal abnormality.[7 8] An indirect fluorescent test for measuring serum anti-*Toxoplasma* IgG titre was negative in this patient at 1 in 10 dilution. Desmonts[11] emphasised the importance of calculating the ratio of the antibody titres between aqueous and serum to make the diagnosis. We did not perform anterior chamber paracentesis since we thought it was invasive and might be harmful to the patient. Though the negativity of the serum antibody test did not exclude the presence of a *Toxoplasma* infection the association with peculiar retinal changes in this case revealed that it was unlikely that the macular lesions were due to a previous *Toxoplasma* infection.

Pigmented paravenous retinochoroidal atrophy is characterised by the presence of perivascular, predominantly paravenous, aggregations of pigment clumps associated with peripapillary and radial zones of chorioretinal atrophy and is thought to be degenerative in origin.[12-15] Though some parts of the retina in this patient showed chorioretinal atrophy the marked perivascular pigment aggregations and chorioretinal atrophy were similar to that of the disease.

The present case showed a bilateral macular coloboma with the perivascular existence of pigment clumps that seemed to result from a common insult affecting their developmental process and could not be explained by a single *Toxoplasma* macular lesion. The *Toxoplasma* IgG antibody test was negative in this patient. Though the aetiology of this case is still unknown the presence of a bilateral macular coloboma, pigmented paravenous retinochoroidal atrophy, and negative laboratory examinations lead us to speculate that it is a developmental abnormality in nature.

The authors thank Miss L S Yen for typing and preparing the manuscript.

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British Journal of Ophthalmology, 1992, 76, 252–253

Metastatic endophthalmitis caused by *Clostridium perfringens*

Vinay Nangia, Colin Hutchinson

Abstract

A case of metastatic endophthalmitis due to *Clostridium perfringens* originating from the biliary tract is reported. The grave visual prognosis and the importance of early detection and treatment of the primary source of infection are emphasised.

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Accepted for publication 20 September 1991

Case report

A 65-year-old man presented with a 24-hour history of loss of vision in the left eye. The eye had become red and the lids swollen. During the preceding week, he had suffered severe colicky pain in the right hypochondrium. Past medical history was unremarkable.

On examination the patient was apyrexial and appeared well. His right eye was normal with a visual acuity of 6/5. His left eye had no light perception. The lids were swollen and indurated. There was complete ptosis and 5 mm of proptosis. All ocular movements were grossly restricted. The conjunctiva was congested with subconjunctival haemorrhage. The cornea was oedematous with severe Descemet's folds and many large keratic precipitates. The anterior chamber was shallower than in the fellow eye, with cells and flare. The pupil was fixed and dilated. There was no red reflex. The intraocular pressure was 50 mm Hg. He was commenced on intramuscular Magnapen 500 mg four times daily and gentamicin 80 mg three times daily. Oral acetazolamide 250 mg four times daily was given. Gentamicin and methicillin were injected in the subconjunctival space. Topical chloramphenicol hourly, atropine 1% twice daily, and betamethasone four times daily were started.

Investigations were as follows. The ESR was 70 mm/hour. A leucocytosis of $13{\cdot}2\times10^9$/l with 90% neutrophils was noted. Serum electrolytes and liver function tests were normal, as was the chest *x* ray.

On the following day proptosis and corneal haze had increased. Details of the anterior chamber were obscured. Cultures from the conjunctiva, urine, and blood were sterile. Ultrasound examination (Figs 1 and 2), performed 24 hours after presentation, showed gross thickening of the choroid, with a large collection of subretinal fluid in the inferotemporal quadrant. Later in the day the globe perforated at the limbus. Evisceration was performed. The evisceration specimen grew a massive culture of *Cl perfringens*, sensitive to metronidazole, penicillin, ampicillin, and cloxacillin. The patient was treated with intravenous benzylpenicillin 600 mg four times daily.

Ultrasound examination of the abdomen confirmed an enlarged gall bladder. A laparotomy performed 9 days after presentation, revealed an acutely inflamed gall bladder. Within the bladder were multiple stones and debris, and the mucosal surface had several ulcers. The bile was sterile, probably due to the antibiotic treatment. The recovery from surgery was uncomplicated.

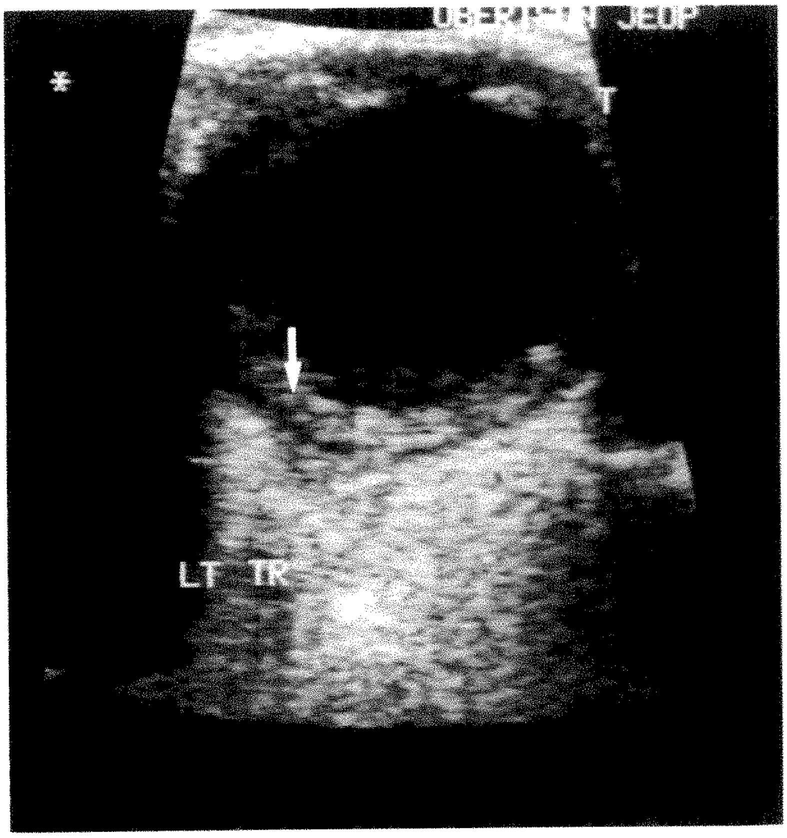

Figure 1 Ultrasound of left eye, 24 hours after presentation, showing gross thickening of the choroid.

Discussion

Cl perfringens produces a particularly vicious suppurative panophthalmitis. In an extensive review of 56 cases Leavelle[1] described the following signs and symptoms to be typical of gas gangrene panophthalmitis. Pain and rapid loss of vision within 12 hours following injury. Proptosis, hypopyon, ring abscess of the cornea, coffee-coloured discharge, gas bubbles in the anterior chamber, rise in intraocular pressure, immobilisation of the globe, and total loss of fundus reflex, all usually evident by 24 hours. All 56 cases followed penetrating injuries to the eye. In every case there was total loss of vision, and the eye was removed.

Since then two cases have been reported,[2,3] where the eyes have been saved following anterior chamber infection by *Cl perfringens* following penetrating injury. The first responded to removal of foreign body and systemic antibiotics,

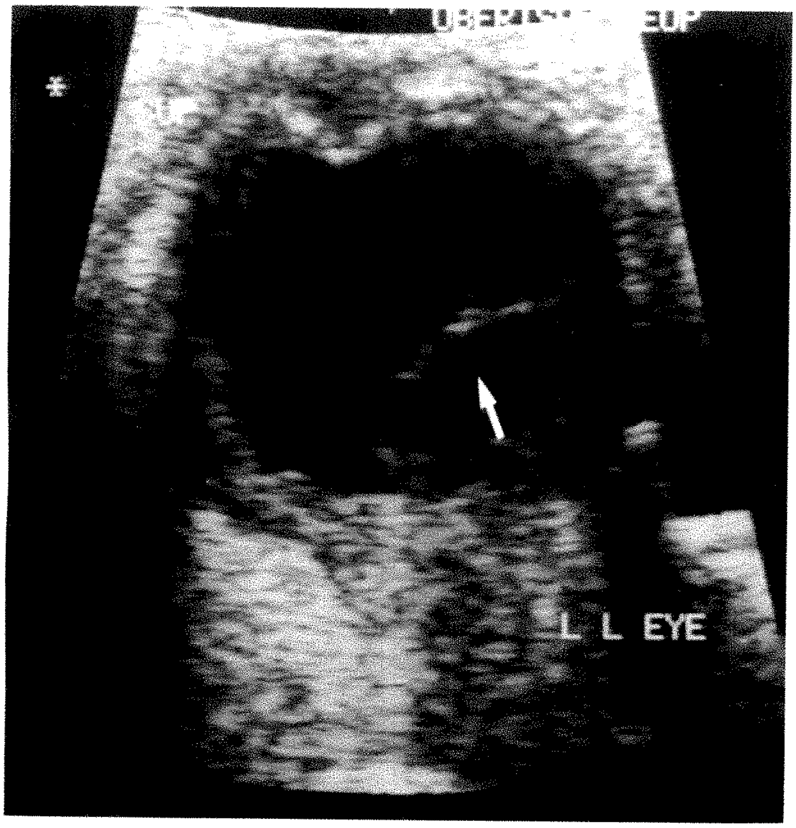

Figure 2 Ultrasound of left eye, 24 hours after presentation, demonstrating subretinal fluid.

and the second underwent debridement of anterior chamber with vitrectomy instrumentation and systemic antibiotics. In both cases there was no definite evidence of vitreous involvement.

The patient in our report did not suffer a penetrating injury. All findings suggested a metastatic infection arising from the biliary tract. Despite this difference, the course of panophthalmitis was generally similar to that described by Leavelle.[1]

The only previously reported case of endogenous *Cl perfringens* panophthalmitis also arose from a biliary infection in a 68-year-old man.[4] A gross haemorrhagic retinopathy was visible before the fundal view was lost. The loss of vision was rapid and complete. The gall bladder perforated despite surgical drainage and systemic antibiotic therapy with chloramphenicol, ampicillin, gentamicin, and methylprednisolone given parenterally. Death resulted from clostridial septicaemia.

No form of treatment has ever been demonstrated to alter the devastating progression of *Cl perfringens* infection with vitreous involvement. Systemic and subconjunctival antibiotics have not succeeded.[1] Intravitreal penicillin was shown to be beneficial in experimental infection in rabbits[5] and should be considered in conjunction with early vitrectomy. The importance of a vitreous tap to aid in the diagnosis, as in any endophthalmitis, cannot be overemphasised. Clinical experience in the efficacy of vitrectomy in clostridial infections is non-existent because of the rarity of its occurrence and the fulminating course. However it should be a serious consideration if the eye can be salvaged. Endogenous endophthalmitis in comparison with exogenous endophthalmitis may be more difficult to salvage even with an early vitrectomy due to the vascular route of spread of *Cl perfringens* within the eye, and the attendant damage to the vascular and neural tissue of the choroid, retina, and optic nerve caused by its toxins.

Although the prognosis for the eye is poor early recognition of this condition is vital, so that the source of infection can be detected and treatment instituted urgently in this life threatening situation.

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LETTERS TO THE EDITOR

Peribulbar anaesthesia

SIR,—Joseph *et al*[1] report a case of globe penetration occurring as a complication of peribulbar anaesthesia. They highlight the potential risks of this procedure which have been previously reported.[2-4] They also advocate the use of short blunt needles and the possible use of subconjunctival administration of the anaesthetic in order to minimise the risk of globe penetration. Although the case presented does indeed demonstrate the possible hazard of peribulbar anaesthesia the authors fail to provide any convincing evidence to support their proposals.

The length of the needle used in the presented case is irrelevant as the penetration occurring at the equator could still have been caused by a shorter needle. Although the use of a shorter needle has been described[4,5] and should reduce the likelihood of posterior entry and exit wounds (as occurred in the series examined by Duker *et al*[2]) and optic nerve injury[6]; penetration at the equator and anterior to this region will not be prevented if the needle tip is misplaced. Even in the emmetropic patient it is usually possible to indent the equatorial retina, for the purpose of funduscopy, by pressure on the skin surface. It is then easy to imagine the length of needle required to traverse the distance between skin surface and equatorial retina being less than 2 cm.

The lack of sharpness of the Atkinson needle in the case presented did not prevent globe penetration. Indeed it is possible that the blunt tip actually compresses the tissues ahead of the tip thus giving a misleading impression of depth of injection.

The equator of the globe, with the eye in the primary position, is the greatest diameter in the coronal plane. Any needle entering the orbital region anteriorly must be directed in such a manner as to avoid encountering the sclera. Only by accurately judging the position of the equator can a needle be inserted in safety. A technique of indentation, via skin or conjunctiva, can be used to judge the limits of the globe and, if uncertain, examination of the retinal indentation just prior to the injection could confirm the identification of the equator.

The use of the subconjunctival route for local anaesthesia has been described[7,8] as a satisfactory method, and could be expected to lead to a reduced risk. Unfortunately even this still carries some risk of penetration as illustrated by Yanoff,[9] and the length of the needle is even less important in this technique as there is less tissue for an errant needle to traverse before reaching the globe.

In summary this case indeed confirms the findings of others[2,3] that peribulbar injections may be dangerous, despite the advantages over the retrobulbar route.[10,11,12] However it is doubtful that a shorter needle would have prevented penetration – in this case of globe penetration. The blunt needle has been shown here to have its limitations; in addition subconjunctival injection does not virtually eliminate risk of penetration as stated by Joseph *et al*. Surely one can only draw the conclusion that all needles in the orbit are potentially hazardous in the wrong hands, and that careful supervision and training in technique have far more relevance than the type of needle used in the administration of local anaesthesia prior to ocular surgery.

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Reply

SIR,—Our purpose in reporting this case was to highlight the risks of peribulbar anaesthesia, a procedure which has been said to have a low risk of globe perforation. Since our report went to press additional cases have been described,[1,2,3] suggesting that perforation of the globe due to peribulbar anaesthesia occurs more frequently than was previously supposed.

The length of a normal globe from anterior cornea to the macula is approximately 2·5 cm, the distance to the equator about half this, and it is of course possible to penetrate the globe posterior to the equator with very short needles indeed. A short needle is recommended for peribulbar injections for a number of reasons. Firstly, a 2 cm needle is more than long enough for the job. Secondly, a needle of this length should make injury to the optic nerve and injection of anaesthetic into the subarachnoid space impossible. In addition the risk of injury to the other nerves and vessels in the orbit should be reduced. Thirdly, a short needle should reduce the risks of posterior perforations of the globe as it is unlikely to penetrate sufficiently deeply for this to occur. Fourthly, a short needle affords greater sensitivity to the position of its tip than a long one as anyone who has used intravenous cannulas will attest. A greater awareness of the position of the needle tip should reduce the risk of globe penetration. A blunt needle is recommended as it is less likely to penetrate the globe than a sharp needle although in the myopic sclera described in our report this was clearly not the case. Blunt needles are also recommended as they afford greater sensitivity to the tissue planes, thereby providing the operator with further information about the position of the tip of the needle.

Mr Hawksworth rightly points out that all sharp needles should be used with care and caution around the eye. We believe that this would have no role in making orbital anaesthetic injections safer.

While clearly the subconjunctival route for injection of anaesthetic is not without some risk it must be safer to introduce a needle under direct vision below the conjunctiva rather than to direct it 'blindly' into the orbit.

We would also like to point out that the peribulbar anaesthetic in our case was administered by an experienced, well trained ophthalmologist who subsequently performed the surgery. We believe the complication of globe perforation could happen to any surgeon and merely reflects the hazards of needles in the orbit. The use of a short blunt peribulbar needle would be expected to reduce the risk of globe penetration but not eliminate it altogether, even in the most skilled hands.

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1 Duker JS, Belmont JB, Benson WE, *et al*. Inadvertent globe perforation during retrobulbar and peribulbar anesthesia. *Ophthalmology* 1991; **98**: 519–26.
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The continuing challenge of ocular leprosy

SIR,—Always I read with great interest Mr T J ffytche's articles and comments on ocular leprosy and I appreciate his views. However, he writes in his mini review[1] 'Recent work by Hogeweg *et al*[2] on the relationship between the position of facial patches during erythema nodosum leprosum (ENL) reactions, and the subsequent development of lagophthalmos has considerably helped to identify those patients most at risk.' This quotation may cause confusion because this article deals with type I (reversal) reactions. ENL reactions have neither relationship with facial patches nor with lagophthalmos.

Secondly, corticosteroids are generally considered as the treatment of choice in reversal reactions. The use of clofazimine is controversial and thalidomide is considered to be ineffective in reversal reactions.[3,4]

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Reply

SIR,—I quite agree with Dr Hogeweg's comments concerning the relationship of facial patches with leprosy reactions and lagophthalmos. This occurs exclusively in the type I (reversal) reaction, and not in ENL. This was an error in the text for which I apologise. The treatment in this acute situation consists of systemic steroids to suppress the reaction. High doses of clofazamine and thalidomide have been tried in cases where steroids are unobtainable or contraindicated but their action is too slow and they are generally ineffective.

One other error in the article, which escaped both our notice, was the statement that paralysis of the maxillary branch of the facial nerve causes lagophthalmos. This should of course have read 'the zygomatic branch', and I am grateful for this opportunity to rectify this.

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Fluphenazine induced welding arc maculopathy?

SIR,—Powers *et al* have presented the case of a 45-year-old male welding trainee who incurred bilateral maculopathy supposedly due to unprotected exposure of less than 2 minutes' duration to a manual metal arc welding unit.[1] They believe that fluphenazine, which had accumulated in his retinal pigment epithelium (due to 10 years' treatment for depression), rendered him particularly susceptible to retinal damage.

The authors further state that 'one of the unusual features of this case is that though the patient was only welding for two minutes he developed a bilateral maculopathy without any evidence of a keratitis'. In the early part of the paper they mention that 'there was no accurate record of the exact duration of exposure'.

Is it not possible then, that: (1) the exposure might have been actually longer than 2 minutes; (2) fluphenazine may have accumulated in corneal tissues but rendered them more resistant to photic damage thus explaining the lack of keratitis in the presence of maculopathy?

This paper inspires one to conduct an experimental study on animals put on long term fluphenazine. Noting any accumulation of the drug in corneal tissues and the thresholds for photic keratopathy seems in order.

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[1] Power WJ, Travers SP, Mooney DJ. Welding arc maculopathy and fluphenazine. *Br J Ophthalmol* 1991; 75: 433–5.

Reply

SIR,—In reply to Dr Neki's letter we would like to make the following points:

(1) Although there was not an exact record of the involved exposure time both the patient and the instructor were quite sure that the exposure duration was no longer than 2 minutes.

(2) Dr Neki suggests that fluphenazine may have accumulated in the patient's cornea and may therefore have rendered it more resistant to photic damage. He further suggests that this may then explain the lack of keratitis in the presence of maculopathy. However the literature would suggest otherwise. In a study on the concentration of phenothiazines in the eye of experimental animals Potts[1] has shown that the concentration of prochlorperazine in rabbit cornea is less than 100th that of the concentration in choroid. He found similar results when he looked at the ocular distribution of phenothiazine in hamsters. It would seem unlikely, therefore, that fluphenazine – a phenothiazine derivative – would accumulate in corneal tissues to a significant degree.

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D J MOONEY
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Ireland

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[1] Potts AM. The concentration of phenothiazines in the eye of experimental animals. *Invest Ophthalmol* 1962; 1: 522–30.

BOOK REVIEWS

Vascular Disorders of the Ocular Fundus. By Rodney Grey. Pp 118. £47·50. Butterworth: London, 1990.

The purpose of this book is to demonstrate in colour the photographic appearances of a variety of retinal conditions not all, it has to be admitted, strictly 'vascular' in origin although, in the retina, vessels of some sort are rarely far away.

The book is a great success. After preliminary general observations on normal anatomy and pathology, methods of examination, principally fluorescence angiography, and the effects of treatment with photocoagulation, the book then covers each condition separately.

A fairly brief but very much to the point description is accompanied by well chosen and beautifully reproduced illustrations. The writing is lucid and therefore a pleasure to read. Afficionados of retinal disease might perhaps question some parts in detail but the average general ophthalmologist, and certainly all postgraduate students, will find the simplicity and clarity of the text most enlightening.

It is traditional to find a few faults. There are a few minor proof reading errors, such as the rather jolly mis-spelling of Dr Dollery's name on pp 6, 12 and 18 and possibly a transposition of two photographs on p 66.

In summary this book is highly recommended.

REDMOND SMITH

Angle-Closure Glaucoma. By Stanley Hyams. Pp 186. Dfl 90.00. Kugler: Amsterdam, 1990.

This small book covers the subject of angle-closure glaucoma in an original and informative manner with special attention paid to the bibliography on which the current understanding of angle-closure glaucoma is based. The major difference between this book and standard texts on the subject is that each chapter is composed of approximately equal portions of text and the author's own abstracts of the papers from which this knowledge has been drawn. This original style of presentation will appeal more to the reader with a specific interest in angle-closure glaucoma than perhaps an ophthalmologist in training who wishes to gain a rapid and easily remembered understanding of the subject. However, this style does allow the reader to cover a very wide range of references quickly without a visit to the library, and makes very interesting reading. It is salutary to find out just how much of our knowledge and accepted teachings are based on small series of patients and case reports – especially with regard to rarer conditions such as malignant glaucoma.

The book is subtitled 'A comprehensive review of primary and secondary angle-closure glaucoma' and certainly the interested reader will find much useful information which does not appear in standard texts, for example the chapters on 'Prevalence' and 'Biometrics.' Most chapter headings are enlivened with relevant quotations from historical writings which show the astuteness and common sense of our predecessors. The author helps to clarify the nomenclature and hence classification of glaucomas associated with narrow and closed angles, and should be applauded for his efforts as accuracy in definition is of such importance. His message on another confused area, that of the role of provocative tests was not quite so clear, however, and the reader is given a rather ambivalent message about their use. In discussing laser iridotomy the author should have made a clear distinction between argon and Nd:YAG laser iridotomy as the reader otherwise gains the impression that the complications attributed to 'laser iridotomy' are equally common with both lasers.

The lack of illustrations, clinical photographs and diagrams, makes this book appear rather stark and this will detract from its appeal, as the modern reader has come to expect the understanding and reinforcement of ideas that good illustrations give to a text's message. However, the readability of this book and its important content make it a useful addition to an ophthalmic library.

PETER K WISHART

OBITUARY

SATISH KUMAR BHARGAVA,
MB, BS, DO, FRCSE, FCOphth

Satish Bhargava was born in Lahore in 1939 but moved to Delhi with his family in 1947 on Partition. He was one of the first intake of students at the All India Institute of Medical Sciences from which he qualified in 1962. After an internship there he came to England to take up a casualty officer post at Lister Hospital, Hitchin, where he met his future wife.

He started training in ophthalmology at the West of England Eye Infirmary, Exeter in 1963, continued at the Glasgow Eye Infirmary in 1965, and returned to Exeter as Registrar in 1968. He became senior registrar to the professorial unit at Manchester Royal Eye Hospital in 1971 where he became interested in retinal pathophysiology.

On appointment to the consultant staff there in 1975 he developed an electrophysiological diagnostic service and a referral clinic for the management of inherited retinal disorders. Both on his own and in collaboration with the Department of Optometry and Vision Science at the University of Manchester Institute of Science and Technology he was responsible for a steady stream of publications in this field, as well as on colour vision and toxic amblyopia.

In addition to running a very busy unit at MREH, where he was chairman of the medical committee twice (1981–3 and 1987–9), he also developed a close relationship with the Manchester department and School of Orthoptics, of which he was medical director from 1986–9. He frequently examined for the Orthoptic

Society as well as for the Royal College of Surgeons of Edinburgh, the British Optical Association, and the Ophthalmic Nursing Board.

He was a founder member of the Rotary Club of Stockport Lamplighter, where he served with distinction on the international committee. He indulged his interest in the restoration of sight and in children's education by promoting aid for eye camps in India and by sponsoring the education of two African and two Indian children, projects which continue to be supported by the club.

He was highly respected by his colleagues and patients and was a hard-working, unassuming, conscientious doctor and fine surgeon who was always helpful to his patients and colleagues. He bore his final illness with characteristic quiet fortitude and lack of complaint and, on his death in 1991, is survived by his wife, Sandra, and two children, his son having just entered medical school.

A E A RIDGWAY

NOTES

20th Meeting European Strabismological Association (ESA)

A symposium on the management of intermittent exotropia is to be held in Brussels on 22–24 May 1992. There will be free paper sessions and discussions on various topics along with poster exhibits. Further information from: Dr M Spiritus, Department of Ophthalmology UCL, Hippocrate Avenue 10, B–1200 Brussels, Belgium. (Fax: 32–2–764 29 88.)

European Ophthalmic Pathology Society

The 30th Annual Meeting of the European Ophthalmic Pathology Society was held together with the Verhoeff Society in Nuremberg, Germany, 8–12 May 1991 at the invitation of the Organising Secretary EOPS Professor Dr G. O. H. Naumann. Thirty three members of the EOPS and 31 members of the Verhoeff Society attended the meeting. The following papers were presented at the scientific sessions:

- Hepatoblastoma metastatic to the eye. (D. M. Albert, Boston, USA)
- Another eye tumour in a Riesenschnauzer dog. (K. Arnesen, Oslo, Norway)
- Pathologic study of hydrogel implant in corneal stroma of cat. (P. Bec, Toulouse, France)
- Unusual bluish tumours of the eyelid and conjunctiva. (Angioleiomyoma and glomangioma. (M. Boniuk, Houston, USA)
- A case of cryptophthalmos syndrome in a 15-week-old fetus. (A. Brini, Strasbourg, France)
- Discoid lupus erythematosus of the eyelid margin. (J. D. Cameron, Minneapolis, USA)
- Retinal pigment epitheliopathy in the ALS/PD complex of Guam. (R. J. Campbell, Rochester, USA)
- Spindle cell tumour of eyelid in patient with lymphoma. (J. P. Crawford, San Francisco, USA)
- Inherited systemic metabolic disease with corneal involvement. (J. G. Cunha-Vaz, Coimbra, Portugal)
- Merkel cell tumour of the eyelid. (V. T. Curtin, Miami, USA)
- Malignant transformation of a choroidal naevus. A 46 year case history. (B. C. Daicker, Basel, Switzerland)
- Ciliary body and iris metastasis of cutaneous melanoma in a patient with dysplastic naevus syndrome. (D. de Wolff-Rouendaal, Leiden, The Netherlands)
- Melanocytomalytic glaucoma. (R. C. Eagle, Philadelphia, USA)
- Intraocular involvement with subretinal pigment epithelium infiltrates by mycosis fungoides. (P. R. Egbert, Stanford, USA)
- Clinically atypical granular dystrophy with histologic features of lattice dystrophy (Avellino dystrophy): new perspectives. (R. Folberg, Iowa City, USA)
- Recurrent well differentiated orbital liposarcoma with myxoid areas occurring in a teenager. (R. L. Font, Houston)
- Choroidal pneumocystosis. (R. Y. Foos, Los Angeles, USA)
- Granulomatous conjunctivitis. (W. C. Frayer, Philadelphia, USA)
- Fibrous histiocytoma of the lacrimal sac. (A. H. Friedman, New York, USA)
- Lacrimal gland myoepithelioma. (A. Garner, London, UK)
- Peutz-Jeghers-like pigmentation, the presenting manifestation of bilateral diffuse melanocytic proliferation of the uveal track; cancer associated melanocytopathy (CAM). (G. J. Gass, Miami, USA)
- Kimura's disease of the orbit. (G. J. Goder, Berlin-Buch, Germany)
- Epikeratoplasty for keratoconus. (W. R. Green, Baltimore, USA)
- Corneal changes in Peters's anomaly. (R. Haddad, Vienna, Austria)
- Pathology of familial (dominant) exudative vitreoretinopathy) (FEVR) in a newborn and in an infant. (A. Hamburg, Bussum, The Netherlands)
- Walker-Warburg syndrome. (M. Hanssens, Gent, Belgium)
- Posterior polymorphous dystrophy of the cornea. (A. S. Henriquez, Barcelona, Spain)
- Congenital malignant rhabdoid tumour of the eye and orbit. (A. A. Hidayat, Washington DC, USA)
- Ocular inflammatory disease of unknown aetiology. (E. L. Howes, San Francisco, USA)
- Adult extrarenal rhabdoid tumour of the lacrimal gland. (F. A. Jakobiec, Boston, USA)
- Alagille's syndrome (arteriohepatic dysplasia), hepatocellular carcinoma associated with the syndrome in a 4-year-old girl. (O. A. Jensen, Copenhagen, Denmark)
- Chondroma of the orbit. (E. Kock, Stockholm, Sweden)
- Optic nerve astrocytoma with angiogenesis. (G. K. Klintworth, Durham, USA)
- Pseudophakia lipomatosa (PHPV). (E. Landolt, Zürich, Switzerland)
- Orbital carcinoma of unknown origin. (Z. Latkovic, Belgrade, Yugoslavia)
- Malignant fibrous histiocytoma of orbit: infarction of the optic nerve. (W. R. Lee, Glasgow, Scotland, UK)
- Iatrogenic lysosomal storage disease of the cornea. (J. Libert, Brussels, Belgium)
- Giant cell astrocytoma of the retina. (T. A. Makley, Columbus, USA)
- Not-predictable melanoma reaction on empirical radiation doses. (W. A. Manchot, Rotterdam, The Netherlands)
- Lineage and ubiquitination in optic nerve gliomas. (A. C. E. McCartney, London, UK)
- Primary histiocytoid carcinoma of the eyelid. (I. W. McLean, Washington DC, USA)
- Ocular findings in cerebro-ocular dysplasia-muscular dystrophy (COD-MD) syndrome. (C. M. Mooy, Rotterdam, The Netherlands)
- Conjunctival nodule with testicular tumour. (J. Mullaney, Dublin, Ireland)
- Proton beam treated malignant melanoma. (P. Naeser, Uppsala, Sweden)
- Fibrous histiocytoma of the corneal limbus. (G. O. H. Naumann, Erlangen, Germany)
- Castleman's disease in one orbit. (J. U. Prause, Copenhagen, Denmark)
- Torulopsis candida (*Candida famata*) endophthalmitis simulating *P. acnes* syndrome. (N. A. Rao, Los Angeles, USA)
- Atypical Schnyder's dystrophy. (M. M. Rodriques, Baltimore, USA)
- Massive gliosis of the retina. (A. M. Roth, Sacramento, USA)
- Vitreous metastasis from cutaneous melanoma. (J. Sahel, Strasbourg, France)
- Fungus in epiretinal membrane. (M. E. Smith, St Louis, USA)
- A posterior form of macular corneal dystrophy – type 2 (keratan sulphate positive). (W. H. Spencer, San Francisco, USA)
- Conjunctival malignant melanoma. (I. Süveges, Szeged, Hungary)
- Supernumerary eye in multicystic craniocervical abnormality: unilateral diplophthalmus associated with ipsilateral temporoparietal porencephaly, additional tooth and cervical cyst. (F. H. Stefani, Munich, Germany)
- An atypical case of tumour of the eyebrow: melanoma or sarcoma? (M. Sterkers, Paris, France)
- Abnormal scleral collagen in nanophthalmos. (B. W. Streeten, Syracuse, USA)
- Malignant fibrous histiocytoma of the orbit with spontaneous resolution. (A. Tarkkanen, Helsinki, Finland)
- Malignant medulloepithelioma and hydroxyapatite orbital implant. (M. O. M. Tso, Chicago, USA)
- Microphthalmos with orbital cyst. (M. H. Vogel, Göttingen, Germany)
- Honeycomb-shaped corneal dystrophy Thiel-Behnke. (H. E. Völcker, Heidelberg, Germany)
- Iridocyclectomy for malignant melanoma of the ciliary body; risk factors affecting success and failure. (F. C. Winter, Stanford, USA)
- Leber's congenital amaurosis. (H. Witschel, Freiburg, Germany)
- Pseudo-Scheie syndrome; congenital hereditary endothelial dystrophy (CHED). (M. Yanoff, Philadelphia, USA)
- Optic atrophy following retrobulbar haemorrhage. (L. Zimmerman, Washington DC, USA)

The next meeting of the EOPS will be held in Strasbourg (France), June 1992. Professors A. Brini and J. Sahel will act as Organising Secretaries.

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Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd

British Journal of Ophthalmology, 1992, **76**, 257–258

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Aspirin and cataract

The lively debate about the protective effect of aspirin taking on cataract formation continues. In this issue Hankey *et al* looked at the association and concluded that 'results do not support the hypothesis that 300–1200 mg daily aspirin, taken for a few years is an effective cataract prophylactic'.

However, the authors freely admit the limitations of a study which only looked for cataracts among survivors of the trial at a single point in time, not to mention the fact that the study was primarily designed to test the effect of aspirin on transient ischaemic attacks. Thus the sample size was not geared to test the effect on cataract and may have substantially reduced the power of detecting any effect of aspirin on the lens. The numbers of patients actually having surgery was four and three in the control and aspirin groups respectively and such small numbers are insufficient for reliable statistical tests. The small sample size is reflected in the wide confidence intervals.

While there are a number of case control studies showing that aspirin or aspirin-like substances protect against cataract,[1–4] some case control and cohort studies claimed not to have shown any such effect.[5–8] What is the reader to believe?

A problem with case control studies is the ever present possibility that some variables are not allowed for in matching, and the finding of an association is not proof of a causal relationship. Rather, the finding of an association provides a lead for cohort studies, clinical trials, and studies on mechanisms of action. Causation of cataract is multifactorial[9] and it would be surprising if the ingestion of a single substance could protect against all types of cataract. It is, therefore, not surprising that a beneficial effect is not readily apparent in some of the studies.

So far, no work has disproved the association and several of the studies which claim not to show a protective effect, if anything, lend support to it. For example, West *et al*[5] in their article disclaiming the association, actually found a reduced prevalence of cataract in subjects who had used any aspirin at all $(p<0{\cdot}03)$ though no dose-response relationship. There are two large randomised controlled trials whose results have been published, but there are methodological flaws with respect to cataract which have been pointed out by Harding.[10] In the UK trial on physicians[7] there was no placebo group, and aspirin-like analgesics were not denied the controls, many of whom later used aspirin for various reasons. In the Physician Health Study (PHS)[8] involving 22 071 subjects, while the groups were well matched the study was stopped too soon in respect of aspirin taking, when it demonstrated a striking protective effect on non-fatal myocardial infarction but before a significant divergence in the rate of cataract formation in the groups could be demonstrated.

Nevertheless, in the PHS study, the aspirin-taking group did have fewer cataract operations. A further problem with this study is that 'control' subjects had a trial of aspirin or aspirin-like non-steroidal anti-inflammatory agents before commencement of the study in order to minimise noncompliance. In view of the findings of some case control studies that the taking of any aspirin could have conferred some protection, such a preliminary step could have produced a confounding effect.

The exact mechanism of action in preventing cataract is not known, but a plausible theory is the acetylation of lens proteins by aspirin which may protect against glycation[11] and carbamylation.[12] This is presumably the explanation given by protagonists that aspirin taking in the past could confer protection.

Whatever the mechanism the protective effect has yet to be established. Meanwhile, cataract is the commonest cause of blindness in the world and, though operable, treatment is not accessible to the majority of the blind in the developing world. In developed countries cataract is a major drain on resources and poses a problem which the health service is failing to solve.[13] As an age-related problem it can be expected to worsen with an increasingly aged population. One estimate suggested that if cataract could be delayed by 10 years the number of cataract operations needed would be decreased by 40%.[14] Therefore, any hopeful preventive measure deserves to be studied. To date, no study has been reported that was specifically designed to test the effect of aspirin on cataract. In view of the increasing magnitude of the problem to which no solution is in sight, aspirin still deserves a serious look.

HUNG CHENG

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13 Hospital inpatient waiting list 1985–1990 DHSS Statistics and Research Division, Branch SR2A.

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ORIGINAL ARTICLES

Does aspirin affect the rate of cataract formation? Cross-sectional results during a randomised double-blind placebo controlled trial to prevent serious vascular events

UK-TIA Study Group*

Abstract

A total of 2435 patients with transient ischaemic attack or minor ischaemic stroke were entered into the UK-TIA aspirin trial and randomised to treatment with aspirin 1200 mg/day, aspirin 300 mg/day, or placebo. At a single point in time during the trial patients were examined ophthalmoscopically for evidence of cataracts. The length of time that each patient had been participating in the trial at the time of ophthalmic examination varied from 1 to 5 years. The prevalence of cataracts was similar in patients allocated aspirin and patients allocated placebo irrespective of the length of time that they had been in the trial. These findings suggest that aspirin taken in a dose of 300 to 1200 mg daily for a few years does not prevent cataracts.

Aspirin is a remarkable preparation; it relieves our aches and pains, reduces fever, lowers the risk of serious vascular events in patients with symptomatic cardiac or cerebral ischaemia by about a quarter,[1] and it is widely available, inexpensive, and relatively non-toxic. Furthermore it has been claimed recently that aspirin may protect against cataract, the world's leading cause of blindness.[2-10] However aspirin has not been generally accepted as an effective cataract prophylactic because of conflicting data from several other studies.[11-16] In view of the uncertainty about the effect, if any, of aspirin in preventing blindness, and the implications if it were effective, we took an unusual opportunity to test the hypothesis that aspirin reduces the incidence of cataract formation by examining patients towards the end of the United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial.[17] If aspirin prevents cataract then we would anticipate a divergence of cataract prevalence between those allocated aspirin and those allocated placebo, becoming more marked the longer the patients had been in the trial.

Methods

Between 25 July 1979 and 8 October 1985 a total of 2435 patients with a recent transient ischaemic attack (TIA) or minor ischaemic stroke entered the UK-TIA aspirin trial and were allocated at random to receive aspirin 600 mg twice daily, aspirin 300 mg once daily, or matching placebo. The trial methods have been published elsewhere.[17] During 1984/85 surviving patients still attending hospital for follow-up ($n=1889$) were assessed for evidence of cataract formation; patients were asked whether they had ever been told that they had a cataract and whether they had undergone cataract removal and, if so, when. The patient was then examined by the neurologist using an ophthalmoscope and cataracts were classified as present or absent.

Results

Table 1 shows the prevalence of cataracts detected ophthalmoscopically in one or both eyes in each of the three treatment groups, the number of cataract extractions performed during the study period up until 1985 among patients in each of the treatment groups, and the number of patients with ophthalmological evidence of cataracts according to the treatment received and the time from randomisation – that is, the duration of treatment. The relative risk of developing ophthalmological evidence of cataracts according to the treatment received and the time from randomisation is illustrated in Figure 1. No significant protective effect is apparent. A separate analysis, excluding those patients who had stopped their trial medication, revealed very similar results.

Discussion

This study is an example of opportunistic research. After more than 2000 patients with non-disabling cerebral or ocular ischaemia had been randomised to treatment with aspirin or placebo they were examined by their neurologist at a single point in time during follow-up to determine whether they had ophthalmoscopic evidence of cataracts or not.

DIAGNOSIS OF CATARACT

The neurologists, who were well trained in the

*Collaborators listed in reference 17.

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Accepted for publication 20 September 1991

Table 1

	Treatment				*Treatment*			
	Any aspirin (n=1268)	*Placebo (n=621)*	*Odds ratio*	*95% Confidence interval*	*Aspirin 300 mg (n=624)*	*Aspirin 1200 mg (n=644)*	*Odds ratio*	*95% Confidence interval*
Cataract (ophthalmoscopic)								
Yes	162 (13%)	81 (13%)	1·0	(0·8 to 1·4)	76 (12%)	86 (13%)	0·9	(0·6 to 1·2)
No	1103	539			547	556		
No eye	3	1			1	2		
Cataract extraction (after randomisation)	4	3			0	4		
	Any aspirin (n=162)	*Placebo (n=81)*	χ^2 *(df=5)*	*p value*	*Aspirin 300 mg (n=76)*	*Aspirin 1200 mg (n=86)*	χ^2 *(df=5)*	*p value*
Time from randomisation to ophthalmoscopic assessment in patients with cataracts (years)								
0–1	20	9			9	11		
1–2	27	11			14	13		
2–3	27	20	3·35	0·65	11	16	2·73	0·74
3–4	36	13			20	16		
4–5	23	13			11	12		
5+	29	15			11	18		

use of an ophthalmoscope and the interpretation of what was seen, were asked to simply state whether a cataract was present or not in either eye based on the appearance of a definite silhouette of the opacity against the background of the red reflex. Standardised diagnostic criteria were not applied because we were not (and still are not) aware of any internationally accepted diagnostic criteria that could be applied easily in a neurology outpatient clinic. Although there may have been some inaccuracies in the diagnosis of cataract these are unlikely to have biased the results because the examiners were not aware – that is, they were 'blind' – of the treatment allocated to the patient. It is likely therefore that any inaccuracies in diagnosis were equally distributed in the aspirin-treated and the placebo-treated groups. Furthermore if the prevalence of cataracts (13%) diagnosed in this population of patients (of mean age 60 (SD 9) years) is compared with the prevalence of cataracts in the 2675 individuals in the Framingham eye study the results were similar. In the Framingham eye study the prevalence of cataracts increased from 4·6% in those between the ages of 52 and 64 years to 46% in those between 75 and 85 years.[18]

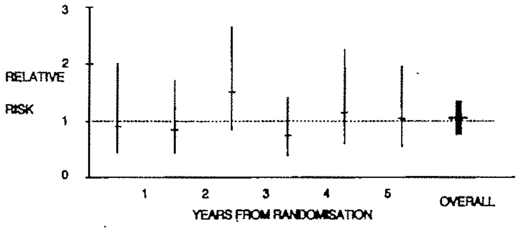

Figure 1 Relative risk (placebo:aspirin) of having ophthalmoscopic evidence of cataracts according to treatment with placebo or aspirin and the time from randomisation to either placebo or aspirin therapy. If the relative risk is greater than 1·0 the prevalence of cataract in patients allocated placebo is greater than in those allocated aspirin. The short horizontal line for each year represents the estimated relative risk and the vertical line the 95% confidence interval of the estimate. The thick horizontal and vertical lines on the right indicate the estimate and its 95% confidence interval respectively of the overall relative risk. As all of the 95% confidence intervals (vertical lines) overlap with a relative risk of 1·0 (dotted line) the result is not statistically significant at the p=0·05 level.

FOLLOW-UP

The time interval between randomisation – that is, entry into the study – and the ophthalmological examination for cataracts varied among the patients from less than 1 to more than 5 years. It is not known whether any cataracts had developed before or after treatment was commenced with aspirin or placebo. However the process of randomisation protects against systematic bias in treatment allocation.

RESULTS

If aspirin has a protective effect on cataract formation it would be expected, in a study of this kind, that the relative risk of having a cataract would be approximately one within the first year of randomisation and, as the time interval from randomisation to assessment increased, the prevalence of cataract formation in the placebo group would gradually increase compared with the aspirin-treated group. This was not the case; there was no significant change in the relative risk over the first 5 years of treatment and no evidence to suggest a time-dependent effect.

CONCLUSION

The limitations of this study are not that the diagnosis of cataract was based upon a relatively crude method (an ophthalmoscope) but that the primary measure of outcome (cataract formation) was assessed at a single point in time only and that the number of patients with cataracts was fairly small, leading to imprecise estimates of relative risk with fairly wide confidence intervals and hence the possibility of a 'false negative' result. Nevertheless the results do not support the hypothesis that 300–1200 mg daily aspirin, taken for a few years, is an effective cataract prophylactic.

This paper was prepared by Dr Graeme Hankey, Dr Susan Richards and Professor Charles Warlow.

The UK-TIA aspirin trial was supported by a grant from the Medical Research Council and the European Aspirin Foundation and Dr Hankey received a grant from the Chest Heart and Stroke Association. We are grateful for helpful comments on the manuscript by Dr P Sandercock, Mr R Peto and Ms B Farrell.

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FIFTY YEARS AGO

Tobacco Amblyopia

In hospital practice, in which tobacco amblyopia is common, the patients do not come from the section of the population in which hard drinking by both sexes, often supported by cheap alcohol, is frequent. These people come to the medical and surgical outpatient departments and exhibit the clinical picture of chronic alcoholism; they do not come to the eye department complaining of impaired vision. If alcohol were an important factor toxic amblyopia would be much more common in women than it is. Tobacco amblyopes are frequently moderate or light drinkers and are often teetotallers.

Br J Ophthalmol 1942; **26**: 43.

British Journal of Ophthalmology, 1992, 76, 262-263

Do patients like day case cataract surgery?

B Davies, A G Tyers

Abstract

One hundred and fifty consecutive questionnaires following day case cataract surgery showed that 87% of the patients would choose day surgery again. The questionnaires were directed at the patients' attitudes to day surgery for their cataracts. There was overwhelming acceptance of the travelling and inconvenience involved.

The visual results and postoperative complications following day case cataract surgery are not significantly different from cataract surgery in hospitalised patients.[1-3]

Each year more patients in Britain are having cataract surgery: the number of elderly people in the population is rising; patients are being operated upon earlier with advances in microsurgery and greater patient demand; and most patients require both eyes to be operated upon.

Day case cataract surgery has been found to be acceptable to patients in a general way,[4] but few previous studies examining patients' attitudes to specific aspects of day surgery for cataracts have been published.[5]

Materials and methods

One hundred and fifty consecutive questionnaires were collected from 146 patients (four had both eyes operated upon on separate occasions in this study). Sixty were male and 86 female; their ages ranged from 51 to 98 years, mean 73·6 years.

The protocol for day case cataract surgery has remained unchanged since it was introduced in Salisbury in 1987. The patients already listed for cataract extraction are offered day case cataract surgery as they approach the top of the waiting list. They are sent information explaining the meaning of day case cataract surgery and what would be required of them (their own transport and a relative or friend to accompany them on their various hospital visits). If they decline, it is emphasised to them that they keep their place on the waiting list in the usual way. If they accept, they are asked to return an enclosed acceptance form. It is stressed that hospital transport is not available. Patients are omitted from this option if they are insulin dependent diabetics, or on warfarin, or if they are poorly controlled hypertensives. Since all day case cataract surgery is under local anaesthesia, the very deaf, the demented, and those who do not speak English are also excluded.

The patients who accept day case surgery attend a preadmission clinic about 2 weeks prior to admission. They spend 20–30 minutes with the senior house officer, who takes the medical history, performs a general examination, eye examination, keratometry and an A scan, then gives further explanation on procedure, and confirms the date for operation once consent has been taken.

On the day of operation they are admitted on to the day ward having taken a light breakfast and their routine medication. Preoperative dilating drops are instilled. No premedication is given.

They are taken on a trolley to the main theatre suite and retrobulbar anaesthesia with facial nerve block is given in the anaesthetic room. No intravenous sedation is given. After operation the patients are taken back to the ward to be collected by their relative(s) or friend(s) 1 hour later, having had refreshments.

During the period of this study the operations were performed by the consultant, senior registrar, or registrar using a standard extracapsular technique and lens implantation.

The patients are requested to return to the clinic the following morning for the first dressing. After slit-lamp examination they are given their postoperative medication to take home. They are then all given a questionnaire to complete at home (Fig 1) and bring back at a later visit.

The patients are reviewed again on the third postoperative day and again 2 weeks later, when the questionnaires are collected. After this there is routine follow-up in the clinic in the standard way.

Results

In this study 70% of patients accepted the offer of day case cataract surgery. Analysis of the completed questionnaires showed that 93% found no problem with the journey to hospital. In 43% the journey took less than half an hour; 55% said the journey took between a half and 1 hour, and only 2% took more than 1 hour. 80% said that, if they had lived twice as far from the hospital, they would still have preferred outpatient surgery.

91% found it no problem to arrange a relative or a friend to accompany them. 13% had no discomfort whatsoever after the operation; 52% experienced a little discomfort only; 31% found it moderately painful; 4% had severe pain. 93% of patients found that paracetamol was sufficient to control the discomfort. 89% had no problems cleaning the eye at home (after the first dressing). 87% said that, if they were to have the operation again, they would prefer it as an outpatient.

There were no significant comments by the patients that added anything to the results of the questionnaires.

Discussion

The recent reports on day surgery of the Audit Commission[6] and the NHS Management Executive Value For Money Unit[7] strongly support an expansion of day surgery in most surgical special-

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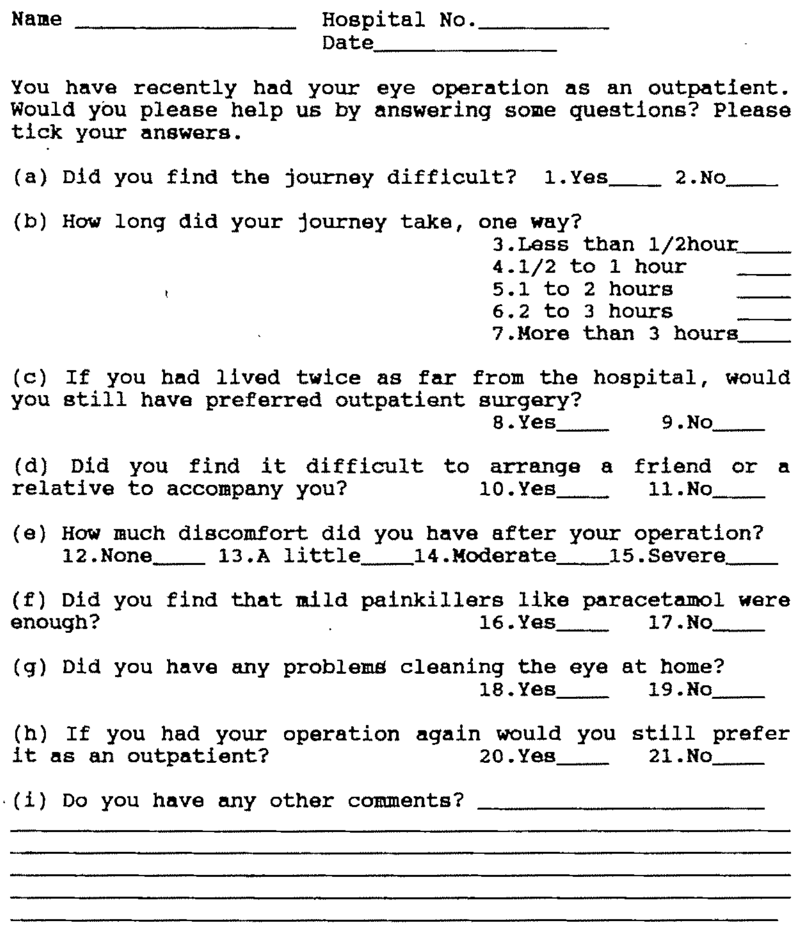
Accepted for publication 14 November 1991



Name ________________ Hospital No.__________
Date______________

You have recently had your eye operation as an outpatient. Would you please help us by answering some questions? Please tick your answers.

(a) Did you find the journey difficult? 1.Yes____ 2.No____

(b) How long did your journey take, one way?
3.Less than 1/2hour____
4.1/2 to 1 hour ____
5.1 to 2 hours ____
6.2 to 3 hours ____
7.More than 3 hours____

(c) If you had lived twice as far from the hospital, would you still have preferred outpatient surgery?
8.Yes____ 9.No____

(d) Did you find it difficult to arrange a friend or a relative to accompany you? 10.Yes____ 11.No____

(e) How much discomfort did you have after your operation?
12.None____ 13.A little____14.Moderate____15.Severe____

(f) Did you find that mild painkillers like paracetamol were enough? 16.Yes____ 17.No____

(g) Did you have any problems cleaning the eye at home?
18.Yes____ 19.No____

(h) If you had your operation again would you still prefer it as an outpatient? 20.Yes____ 21.No____

(i) Do you have any other comments? ____________________

Figure 1 Questionnaire.

ties. The Audit Commission includes cataract extraction with lens implantation in its 'basket' of 20 procedures most likely to be done in a day surgery unit. In ophthalmology as well as other surgical specialties there is likely to be an increasing demand from purchasers for day case surgery for suitable procedures. Although the cost of the surgery is generally unchanged, there are some savings, particularly in nursing salaries. Clinical outcomes have been shown to be as good as under inpatient care. In addition, an integrated day surgery facility offers a service which can avoid cancellations to a greater degree than is possible with inpatient care.[6 7] Patients' attitudes to day surgery have not received the same attention as the clinical outcomes,[8 9] and the Audit Commission has recently proposed a questionnaire which could be used to study them.[10]

Patients who are offered day surgery in Salisbury have to arrange their own transport and escort, and they have to return to the clinic for review rather than be visited by a nurse in the immediate postoperative period. Salisbury is primarily a rural area with a resident population of about 125 000. The Health Authority provides hospital services to a catchment population of approximately 185 000. About 40% of all cataract extractions are performed as day cases though at present no designated day surgery unit exists. Although many patients travel from villages some distance away, travelling was not a problem for 93%; 80% would still have chosen day surgery if they had lived twice as far away. 91% had no difficulty arranging to be accompanied. In a recently published report on day case cataract surgery in the urban area around Bristol a similar percentage (82%) would prefer day surgery again. If those expressing no preference are included, 97% were content with day surgery.

Not being in hospital was not found to be a problem by the majority of patients. 89% had no problem cleaning the eye at home after the first dressing had been done in the clinic. Although only 13% had no postoperative discomfort whatsoever, 93% of patients found that paracetamol was adequate to control what discomfort they experienced.

This is a selected group of patients in that some patients are not offered day surgery because of medical or other reasons, and of those who are offered day surgery 30% declined. Of those 70% who requested day surgery 87% would prefer day case surgery again. The reasons given by the 13% of patients not wanting day surgery again were not specified in one-third, but the remainder gave as reasons the difficulty attending all the hospital visits, too short a recovery time before discharge, and being alone at home. Only 2% of the total number of patients objected to local anaesthesia.

More than 75% of all cataract operations done in Salisbury are under local anaesthesia, and the surgery has been found to be only slightly more stressful for the surgeon than with general anaesthesia.

The findings of this study support our overwhelming impression that day case cataract surgery is preferred by the majority of patients. Because of this level of acceptability and the good clinical outcome, demand is likely to increase.

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British Journal of Ophthalmology, 1992, 76, 264–267

The dark perimetric stimulus

Erkan Mutlukan, Bertil E Damato

Abstract

We determined the disappearance eccentricities of dark and bright stimuli of equal size in the inferonasal central visual field using the oculokinetic perimetry technique at different levels of surrounding illumination. The results suggest that a dark stimulus on a bright background has a smaller 'isoptre' than an equally bright stimulus on a dark background, and that variation of ambient illumination and consequent alteration of background luminance have less effect on the visibility of a dark stimulus than a bright one.

The visual field is conventionally examined with a light stimulus on a dark background. This choice of perimetric stimulus probably stems from the assumption that the fundamental role of the retina is to detect light.[1-3] However, the retina is not merely a light sensor but is primarily adapted for the detection of differences, both increments and decrements, in the amount of light in the visual field. The functional organisation and grouping in ganglion cell receptive fields in the retina provides evidence for this. Stimulation occurs only if there is a difference in the amount of light falling on the receptive field centre and on the surrounding area.[4-9] One group of the receptive fields is activated by light falling into the field centre and is therefore called the 'on' type. Conversely, the other group, namely the 'off' type receptive fields, activate the ganglion cell with the cessation (decrement) of the light.

It is believed that the visibility of a perimetric stimulus is related to the number of overlapping receptive fields in the corresponding part of the retina, which is in turn related to the density of the ganglion cells in that region.[10-13] It is now known that nerve fibres from the retinal ganglion cells travel to the visual cortex in two parallel visual pathways, namely 'on' and 'off' systems which remain morphologically, physiologically, and pharmacologically separate until they converge on single cortical neurones.[12 14-20]

In the 25° central visual field most ganglion cell receptive fields (60–75%) have 'on centre' organisation, so that they are stimulated by a light spot on a dimmer background (that is, 'incremental light stimulus') and are inhibited by a central light decrement. Conversely, with 'off centre' ganglion cells, maximal stimulation occurs with a dark stimulus on a brighter background.[5 7 12 15 21] Whereas conventional perimetry tests on-pathway and mainly on-centre receptive fields at various locations across the retina, there may be advantages in testing the off-pathway by a dark stimulus because of the difference in the quantity of reserves in both systems, as it is possible that field defects that are missed with a conventional light stimulus might be detected earlier in certain conditions, such as glaucoma and intracranial disorders affecting the visual system.

The presentation of a dark stimulus on a white tangent screen is difficult, as it would require a white wand which would lead to confusion by casting a dark shadow. This technical difficulty is overcome by using the 'oculokinetic multifixation campimetry technique,' which does not require the stimulus to be moved on the screen, because it is the patient's eye which moves instead.[22]

The aim of our study was to identify differences between responses to dark and light perimetric stimuli in the central visual field by the oculokinetic technique and to determine how these responses vary with changes in ambient illumination.

Material and methods

The study involved the assessment of the visual fields of the right eyes of eight volunteers, six of whom were male and two female. Their visual acuities were all 6/5, and the pupil sizes ranged between 3 and 5 mm in 150 lux room illumination. All eyes were normal.

The experiments were performed with three different types of tangent screen: black, white, and grey, having a light reflectance (albedo) of 5%, 95%, and 50% respectively. Each test stimulus consisted of a disc attached on to the screen which had a light reflectance of either 5% (black) or 95% (white), creating equal but opposite sign luminance (Weber's) contrast at a given illuminance level (Fig 1). The fixation target consisted of a pointer, which was moved across the screen superotemporally by the examiner, so that the pursuit movements of the subject's eye induced a relative shift of the stimulus along the 225° meridian in the central visual field. The eccentricity from fixation at which the stimulus was no longer seen was recorded. This procedure was repeated five times for each target and illuminance level, and a mean value was taken as the final result.

The tangent screen was illuminated with a white light halogen lamp fitted with a diffuser and a dimmer switch which was positioned at 2 metres from the screen. The illumination of the screen was measured and adjusted with a luxmeter (Solex SL100). Every time the ambient illumination was altered, 3 minutes were allowed to elapse before the examination was begun so as to ensure the subject's retinal light adaptation had taken place. The subject was seated, with the head resting on a chin rest so that the right eye was 150 cm from the screen. The left eye was covered with an occluder. All perimetric examinations were performed by the same individual, and all tests for each subject were completed on the same day.

Meridional hill of vision to dark and bright

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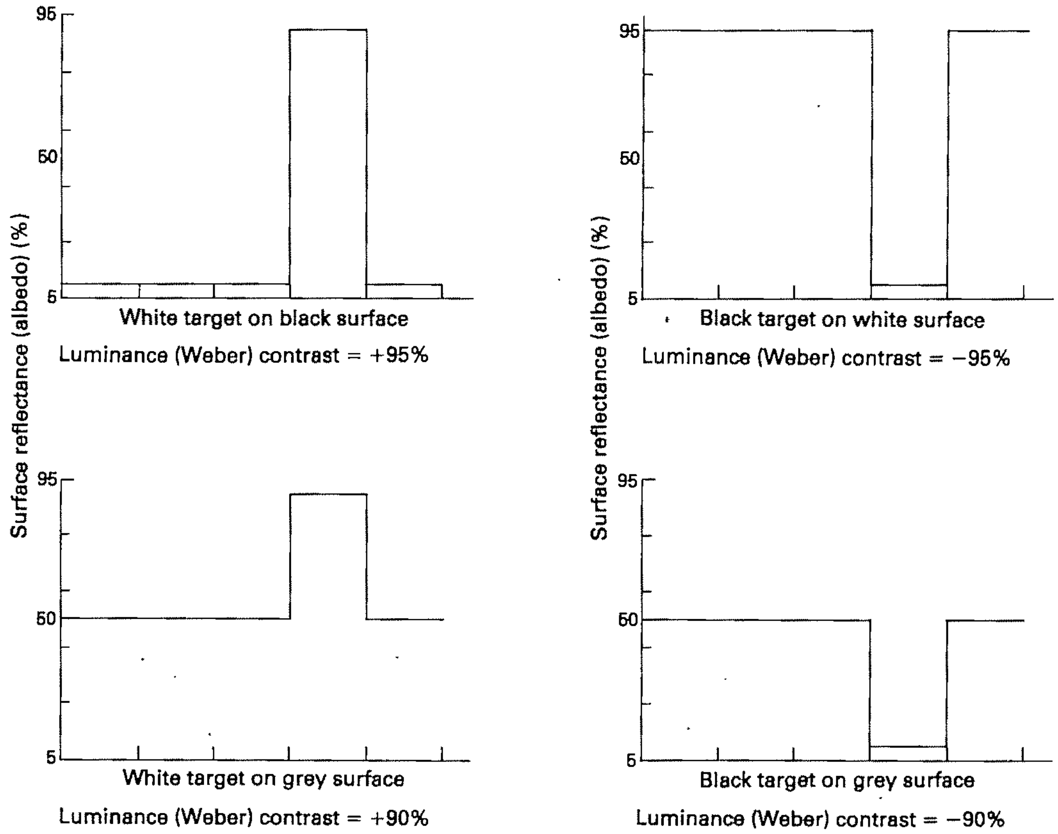
Accepted for publication
21 November 1991



White target on black surface
Luminance (Weber) contrast = +95%

Black target on white surface
Luminance (Weber) contrast = −95%

White target on grey surface
Luminance (Weber) contrast = +90%

Black target on grey surface
Luminance (Weber) contrast = −90%

Figure 1 Luminance profiles and contrast values of four target-background combinations employed in the study. Luminance (Weber) contrast=$(L_{Target}-L_{Background})/L_{Background}$ *(L=luminance).*

stimuli. Four volunteers (two males and two females; mean age 30 years, range 28–31 years) were tested with each of five black stimuli (1, 2, 3, 4, and 5/1500 mm) against a white background, and also with white targets of the same size on a black background. The ambient illumination was 150 lux. The peripheral visibility of both stimulus types on the 225° meridian was compared.

Effect of variation in illumination on dark and bright stimuli. The effect of variation in ambient illumination on the eccentric visibility of black and white stimuli on the 225° meridian was examined at two levels of illumination, which were 13 and 400 lux (that is, a difference of 1·5 log units).

Eight volunteers (mean age 30 years, range 25–39) were tested with each of the following four stimulus-background combinations in a random order: white-on-black, black-on-white, white-on-grey, and black-on-grey. The grey background was employed in order to neutralise the difference in retinal light adaptation levels to different backgrounds, and to establish whether the results were due to the stimulus or the background. In each case a 1/1500 mm (2·5 min) stimulus was employed. The percentage change in stimulus visibility with change in illumination was calculated with the formula:

$$[(I-i)/i]\times 100,$$

where I is the isoptre at 400 lux and i is the isoptre at 13 lux. The percentage change in the isoptre of the black stimulus was compared with that of the white stimulus by the paired t test.

Results

Comparison of visibility of black stimuli on white background and white stimuli on black background. The disappearance eccentricities of the black stimuli in the meridian tested were significantly smaller than those of the white stimuli, the difference being more pronounced with the smaller stimulus sizes (paired t test, $p<0{\cdot}0001$) (Fig 2).

Effect of variation of illumination on black and white stimuli. The percentage increase in white-on-black stimulus disappearance eccentricity was significantly more than that of black-on-white stimulus (t test, $p=0{\cdot}014$). Increasing the ambient illumination from 13 lux to 400 lux increased the isoptre of the white stimulus by 59% and the isoptre of black stimulus by 36% (Fig 3a).

Similarly, the eccentric visibility change due to illuminance variation was significantly more for the white-on-grey stimulus than the black-on-grey stimulus (t test, $p=0{\cdot}0016$). At the higher ambient illumination, the black and white stimuli disappearance eccentricities increased by 75% and 117% respectively (Fig 3b). Isoptre increases of lower contrast black-on-grey stimulus and white-on-grey stimulus were significantly more pronounced than those of black-on-white (t test, $p<0{\cdot}0001$) and white-on-black stimuli (t test, $p=0{\cdot}0069$).

Discussion

The campimetry was performed by the oculokinetic technique so as to be able to use a fixed

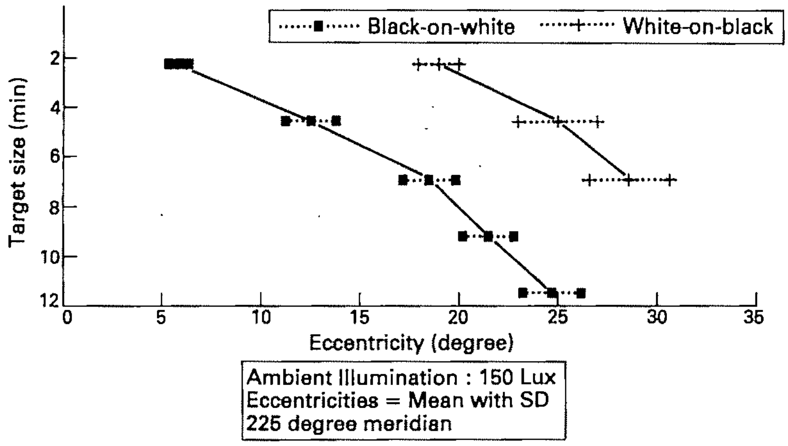


Figure 2 Peripheral visibility of various sizes of equal dark and bright stimuli in the inferonasal visual field (meridional hill of vision). The dark stimuli are significantly less visible than the bright stimuli of equivalent size.

test stimulus, thereby eliminating the need for manually moving the stimulus using a wand, which would have caused a shadow on the background, and which could also have resulted in tilting of the stimulus. A moving fixation target was used instead of several printed numbers on the screen, as previously described, so as to prevent bias caused by the patient memorising the numbers associated with disappearance of the stimulus.[22] Contrary to routine conventional practice, the stimulus moved centrifugally. Although it is well known that isoptres are different when the direction of stimulus movement is from seen-to-unseen compared with unseen-to-seen, pilot studies had indicated that, when the percentage change in isoptre eccentricity is considered according to the above mentioned formula, the same results were obtained whether the location of appearance or disappearance of the stimulus was determined.

One of the principal findings of this study was that the eccentric visibility of black stimuli was less than that of white stimuli of equivalent size. There are several possible explanations for this phenomenon. Firstly, light scatter from the bright surface into the adjacent dark surface on the campimeter may have caused geometrical change in the perceived sizes of the stimuli, the apparent size of the black stimulus being smaller compared with the white stimulus. Secondly, the light stimuli moved through relatively dark adapted, and correspondingly more sensitive parts of the visual field than the dark stimuli, which were presented to bleached parts of the retina. This explanation is implausible in view of the fact that the black stimulus was less visible than the white one even with a grey background. Furthermore, the phenomenon was observed under photopic conditions.

An alternative explanation for the reduced visibility of the dark stimulus may be the fact that it depended mainly on off centre ganglion cells, which in the central field are less abundant than on centre ganglion cells (that is, in a ratio of approximately 1–2:3). Similar psychophysical differences between these two parallel visual pathways have previously been reported for foveal vision with regard to target detection rates and reaction times.[23 24] In addition, electrophysiological differences between these two channels have been observed.[25 26] We are unaware of a previous report of perimetric asymmetries between on and off pathways. If the black perimetric stimulus is indeed testing the off pathway, it may prove to be superior to conventional luminous stimuli. Glaucoma, for example, is believed to affect the peripheral contrast sensitivity, which is the functional result of the balance between on and off pathways.[19 27 28]

The second finding of this study was that the visibility of the black stimulus was perceived by the subjects as being more constant under varying lighting conditions than that of the white stimulus. This difference was observed even when the same grey background was used for both stimuli. One reason for this finding may be that at the two different levels of illumination the differences in the amount of the light reflected by the black and white stimuli surface were not constant. However, both type of stimuli maintained the same equal and opposite sign luminance (Weber's) contrast at each illuminance level (Fig 1). Therefore an alternative explanation is that on and off systems may behave differently with changing levels of ambient illumination. The practical significance of this difference is that standardisation of the ambient illumination may be less important when perimetry is performed with dark stimuli on a bright background than vice versa. This would render the dark perimetric stimulus superior to the conventional

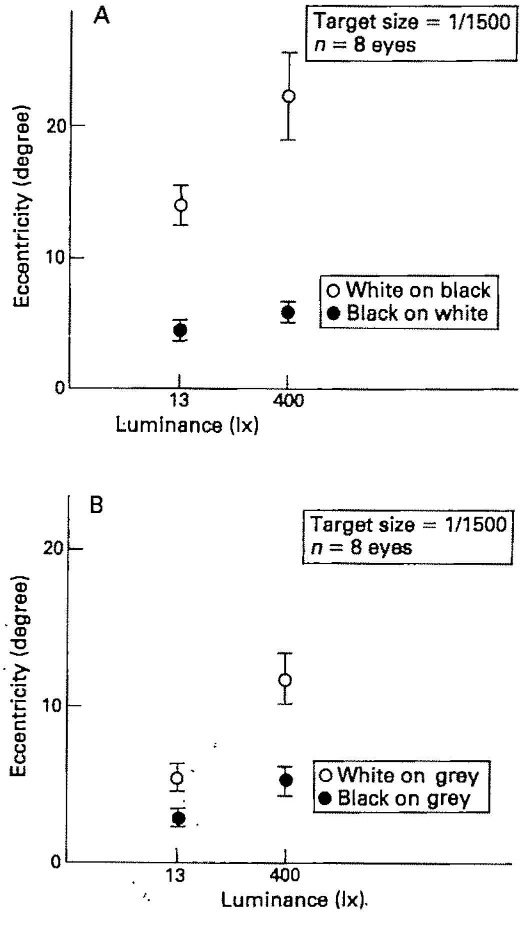


Figure 3A and B The effect of variation in surrounding illumination on the perimetric visibility of equal dark and bright stimuli on tangent screen (mean with SD). The dark stimulus visibility displayed significantly less change with changing level of illumination both on opposite and grey backgrounds. (The illuminance difference is 1·5 log.)

light stimulus when visual field examination is performed in the community and in other situations where it is difficult to maintain standardised and constant lighting conditions.

In conclusion, this study has shown that the black perimetric stimulus is less visible and more stable under variable lighting conditions than the light stimulus. Whether such differences result from the differential stimulation of the on and off visual pathways merits further study.

Dr David Keating helped us on the statistical evaluation of the results. We were financially supported by International Glaucoma Association.

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British Journal of Ophthalmology, 1992, **76**, 268–271

Red eyes in renal failure

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Accepted for publication
17 October 1991

Abstract

Of 57 patients with chronic renal failure who all had deposition of calcium salts in the conjunctival and corneal tissue two developed a brief episode of painful irritation and redness of the conjunctiva and subconjunctiva. This hyperaemia was adjacent to erosions of the corneal epithelium of the eye as a consequence of exfoliation of calcium concretions from the superficial corneal epithelium. Eight patients showed inflammatory reactions of the conjunctivae that were clinically identical to inflamed pingueculae. Three patients showed an inflammatory reaction of the eye that was characterised by a waxy red, more or less diffuse, episcleral and conjunctival hyperaemia extending beyond the palpebral fissure. The average value of the serum calcium concentration in these patients was particularly high and statistically significantly higher than in patients with calcification but without inflammatory signs and also higher than in patients who showed pingueculitis. We propose to reserve the term 'red eye *of* renal failure' for the latter group of patients.

In 1966 Abrams[1] drew attention to the association of irritable red eyes and renal failure in a patient with calcific deposits in the corneas close to the limbus. These deposits were extremely superficial and some had flaked off leaving small eroded areas which stained with fluorescein. The conjunctiva opposite the erosions was hyperaemic. The symptoms and signs were soon relieved by padding of the eye.

One year later Berlyne and Shaw[2] reported on 15 patients with red eyes and severe renal failure associated with raised serum inorganic phosphate and normal or low serum calcium. The illustration of a typical case showed bilateral temporal conjunctival hyperaemia in the interpalpebral area extending from the corneal limbus to the canthi. Their illustration gave the impression of a small elevated focus in the centre of the temporal conjunctiva.

In 1968 Berlyne[3] described another 13 patients with renal failure (three of whom showed conjunctival irritation and injection) who were also associated with high serum inorganic phosphate levels and normal or even low serum calcium levels. There was no further description of the conjunctival hyperaemia. The authors suggested that there was a relationship between the conjunctival redness and conjunctival calcium phosphate salts deposited as microcrystals.

Subsequent studies of Caldeira *et al*,[4] Ehlers *et al*[5] and de Graaf *et al*[6] identified the redness of the conjunctiva in patients with severe renal failure either by description or by diagnosis as conjunctival inflammatory reactions associated with pingueculae. It seems therefore that there are at least two types of red eyes *in* renal failure; but what is the red eye *of* renal failure?

Patients and methods

During a 6 year period a total of 57 patients with terminal kidney insufficiency and on regular haemodialysis were followed for the occurrence of inflammatory complications of the anterior surface of the eye. There were 36 males ranging in age from 23 to 66 years and 21 females ranging in age from 33 to 68 years.

The age distribution of the patients is shown in Figure 1. The average age was 49 years and the average weight was 69·5 kg. In all patients a complete routine ophthalmic examination was carried out and repeated at periodic intervals. The corneoconjunctival depositions were graded according to the criteria of Porter and Crombie.[7]

Levels of serum calcium and inorganic phosphate were measured every 3 months in each patient and at the beginning of the development of inflammatory reactions of the outer surface of the eye. Fifty healthy persons, matched in sex and comparable in age and weight, were used as controls. As a parameter of kidney function the creatinine clearance was calculated in every patient on the basis of the level of serum creatinine and weight with the formula of Cockroft and Gault.[8] The statistical test used was analysis of variance.

Results

TYPES OF RED EYES

Three distinct types of inflammatory reactions were observed in the patients during this period. In two patients irritation and local hyperaemia

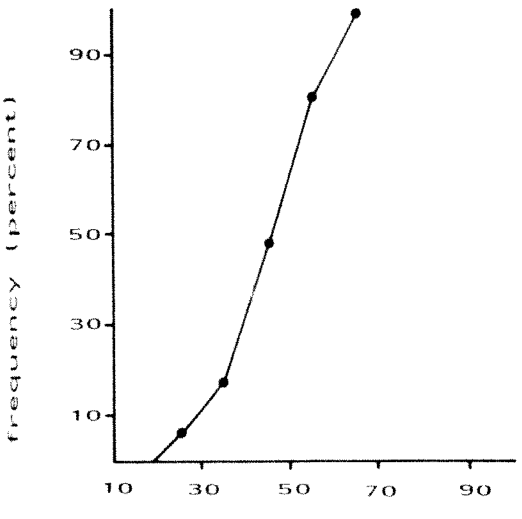

Figure 1 Cumulative frequency distribution of age in 57 patients with chronic renal failure.

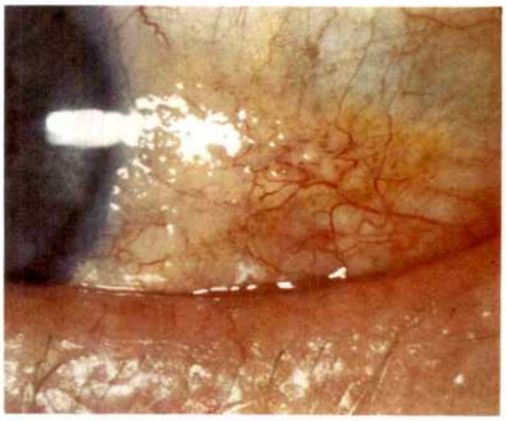

Figure 2 Localised hyperaemia around a raised greyish area of the bulbar conjunctiva in chronic renal failure. Clinically these lesions are indistinguishable from inflamed pingueculae.

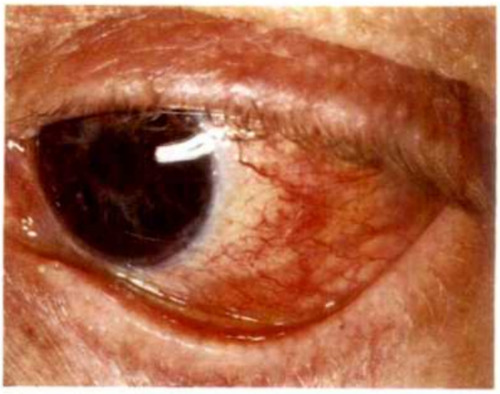

Figure 3 More or less diffuse waxy red hyperaemia of the episcleral tissue and the conjunctiva over it extending beyond the palpebral fissure in patients with renal failure having strikingly high serum calcium concentration.

developed, with pain and photophobia, adjacent to erosions of the corneal epithelium which developed as a result of exfoliation of very superficially deposited calcium salts in the peripheral corneal epithelium in the palpebral fissure. These erosions stained with fluorescein. Signs and symptoms disappeared rapidly after dressing of the eye. These lesions were similar to those described by Abrams.[1]

In eight patients a more or less localised redness of the conjunctival vessels of varying intensity, and occasionally mild congestion of the episcleral vessel was observed. This local hyperaemia of the conjunctival vessels developed gradually around a greyish triangular area situated in the bulbar conjunctiva in the interpalpebral fissure usually on either side of the cornea. The hyperaemia was characterised by exacerbations and remissions. Bacterial cultures were negative.

The greyish triangular lesions were studded with yellowish white spots that were occasionally confluent and more conspicuous at the periphery. In all patients both eyes were affected on the nasal as well as on the temporal side of the conjunctiva. The lesions in the latter localisation were more pronounced. All of them did fluoresce in ultraviolet light.[9] Clinically these lesions are indistinguishable from inflamed pingueculae (Fig 2).

In three patients the hyperaemic inflammatory reaction was of a decidedly different nature. In these patients there was congestion of the vessels of the episcleral tissue and of the conjunctiva over it. The congestion presented as a more or less diffuse, episcleral, and conjunctivally somewhat waxy hyperaemia of the bulbar region extending beyond the palpebral fissure (Fig 3). Discharge if at all present was scanty. No pingueculae were observed. The symptoms, itching and burning, were mild. Bacterial cultures were negative. The inflammatory reaction subsided in 4 weeks on average.

GROUPS OF PATIENTS

From all patients four groups can be constructed. Group A consisted of 46 patients with calcium deposits but without any inflammatory reaction of the conjunctiva. This group included two patients with a brief episode of corneal erosions and reflex irritation and hyperaemia of the conjunctiva. Group B consisted of eight patients with calcification and inflammatory reactions associated with pingueculae. Group C consisted of three patients with an inflammatory reaction resembling diffuse episcleritis and associated conjunctivitis. The three patients from the last group after the inflammatory reactions subsided were placed in group D.

CALCIUM DEPOSITS

In all patients a deposition of calcium salts in the subconjunctival tissue and/or cornea was present. The degree of the corneoconjunctival calcifications for the four groups is shown in Table 1. From this table it is apparent that patients who experienced one or the other type of inflammatory reaction had rather dense conjunctival and corneal calcium deposits.

SERUM CALCIUM CONCENTRATION

Table 2 shows the average values and standard deviations of serum calcium and serum phosphate and also the serum calcium and phosphate product in the control group. Data on serum calcium concentration in the several patient groups presented in Table 3 indicated that patients of groups A, B, and C had statistically significantly elevated serum calcium concentrations compared with the control group. This is graphically shown in Figure 4.

Table 1 The number of patients (expressed as a percentage) in each grade at their first visit according to the criteria of Porter and Crombie. In most patients the temporal side of each eye was more affected than the nasal side. In this table the more heavily affected temporal side of the conjunctiva is noted

Grade of calcification	*0*	*1*	*2*	*3*	*4*	*5*
Group A ($n=46$)	0	35	41	20	2	2
Group B ($n=8$)	0	37	25	25	13	0
Group C ($n=3$)	0	0	0	67	0	33

Table 2 The average values and standard deviations of serum calcium and serum phosphate and the serum calcium and phosphate product in 50 healthy persons

	Serum calcium (mmol/l)	*Serum phosphate (mmol/l)*	*Serum calcium* serum phosphate*
Average	2·4122	1·2950	3·1276
SD (n-1)	0·1004	0·1704	0·4568

*Table 3 The blood concentration of calcium (mmol/l) and phosphate (mmol/l), and the calcium phosphate product (Ca*P). As a parameter of the kidney function, the creatinine clearance values (Cr Cl) are shown*

	Group							
	A (n=46)		*B (n=8)*		*C (n=3)*		*D (n=3)*	
Blood concentration	*Av*	*SD*	*Av*	*SD*	*Av*	*SD*	*Av*	*SD*
Calcium	2·49	0·28	2·61	0·27	3·53	0·65	2·41	0·39
Phosphate	1·85	0·65	1·92	0·53	1·92	0·64	1·63	0·44
Ca*P	4·52	1·33	5·02	1·41	6·62	1·62	3·96	1·28
Cr Cl	5·63	1·59	5·70	1·91	5·61	0·54	6·78	2·05

In eight patients from group B with the localised type of redness associated with pingueculae the average serum calcium concentration was not significantly different from the average value of group A, who showed no inflammatory reaction of the conjunctiva. In the small group of patients presenting with a more or less diffuse type of episcleral hyperaemia there were strikingly high serum calcium concentrations in comparison with the other groups and these differences were statistically significant. Patients were treated with aluminium oxide hydrate in a dose of between 4·5 and 6 g daily and the systemic administration of dihydrotachysterol was discontinued. As soon as the serum calcium concentration returned to normal the inflammatory reaction subsided.

SERUM PHOSPHATE CONCENTRATION

In all groups the serum phosphate concentration was statistically significantly higher than in the control group (Fig 5). The serum phosphate concentration between groups A, B, and C however did not differ significantly statistically. The serum calcium and phosphate product was statistically significantly higher in group C and this was because of the markedly elevated serum calcium concentration.

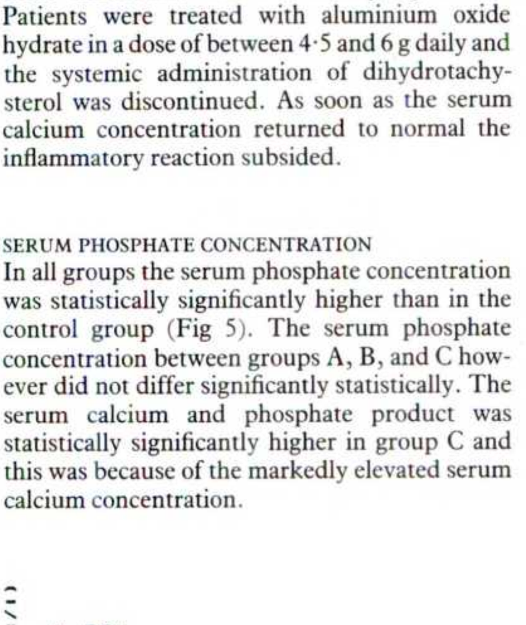

Figure 4 The average serum calcium concentrations with the 95% confidence limits in the four groups and in the control group (CO). The average serum calcium value of groups A, B, and C were statistically significantly higher than that of the control group. The average serum calcium value of group C is markedly elevated and significantly higher than that of groups A and B. The average value of groups A and B did not differ significantly.

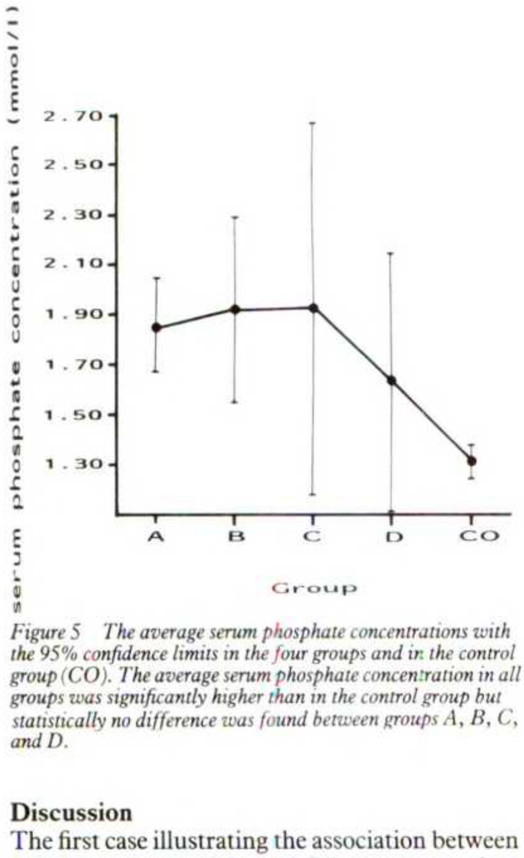

Figure 5 The average serum phosphate concentrations with the 95% confidence limits in the four groups and in the control group (CO). The average serum phosphate concentration in all groups was significantly higher than in the control group but statistically no difference was found between groups A, B, C, and D.

Discussion

The first case illustrating the association between irritable red eyes and renal failure was a patient in whom calcium salts deposited in the corneal epithelium had flaked off resulting in superficial corneal erosions causing painful irritable red eyes which were soon relieved by padding of the eye.[1] This case represented a reflex irritation and hyperaemia and therefore hardly qualifies as a specific ocular disease entity associated with renal failure.

The description of Berlyne and Shaw[2] and Berlyne[3] on the type of the red eye, initially not having a slit-lamp available, was in rather general terms, such as 'conjunctival hyperaemia' and 'conjunctival irritation', and the illustration presented in a typical case seemed suggestive of inflamed pingueculae at the lateral aspects of the bulbus in both eyes. From the description and the illustration of Caldeira *et al*[4] the red eye of renal failure seems identical to inflamed pingueculae, as were the lesions reported by Ehlers[5] and de Graaf *et al*,[6] and therefore cannot be considered a specific disease entity.

These inflamed swellings close to the limbus associated with renal failure cannot be differentiated clinically from inflamed pingueculae not associated with renal failure. The formation of pingueculae is essentially the result of a combination of an age change and of exposure due to the prominent position of the globe in the palpebral aperture. Ehlers considered pingueculae in patients with chronic renal failure as an accelerated age change, a view shared by others[6]; this is also our opinion.

Therefore we propose to reserve the term 'red eyes *of* renal failure' for those rare but specific inflammatory conditions of the anterior surface of the eyes which are characterised by a more or less diffuse waxy red episcleral and conjunctival hyperaemia extending beyond the palpebral fissure with little or no exudate. The lesion is quite unlike the nodular episcleritis or diffuse localised episcleritis periodica fugax. This red eye of renal failure is associated with a disturbance of the calcium metabolism resulting in a high serum calcium concentration. Once the serum calcium concentration returns to normal the inflammatory reaction subsides.

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British Journal of Ophthalmology, 1992, **76**, 272–274

Ulcerative blepharitis in atopic patients – is *Candida* species the causative agent?

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Abstract

A total of 50 patients suffering both from atopic skin disease and different clinical forms of blepharitis have been included in this study. Microbiological investigations (for bacteria and fungi) of the lid margins were performed in all cases. In 21 (42%) of the patients an ulcerative blepharitis which heavily involved the follicles of the lashes was diagnosed. The remaining 29 cases presented with blepharitis of the squamous type. The cultures revealed that 19 of the 21 patients with ulcerative blepharitis were found to grow *Candida* species, whereas fungi could not be detected in any of the other cases of blepharitis. The frequencies of concomitant bacterial organisms found in the cultures were similar in both groups. As atopic patients are known to exhibit a defect in their cell-mediated immunity and possibly also a defective IgA antibody response it is a widely accepted assumption that these immunological changes are contributing factors to the development of a localised inflammation of the lids which is initiated by a variety of micro-organisms. We postulate that when *Candida* species happen to coincide with severe inflammation in atopic patients a blepharitis of the ulcerative type will develop or deteriorate thereby implying that these micro-organisms may play an important role in the development or deterioration of this severe chronic inflammation. It is therefore advisable to perform repeated scrapings and cultures in every case of recalcitrant blepharitis.

Atopic dermatitis is a complex multifactorial skin disease with a spectrum of abnormal immunological and non-immunological findings. A deficiency in T-cell subpopulations, an increased IgE antibody response, and a higher releasibility of vasoactive mediators due to a partial blockade of the ß-adrenergic receptor sites may play a role in its pathogenesis.[1] Since Coca and Cooke[2] introduced the term 'atopy' in 1923, hereditary factors have also been shown to play an important role in the disposition of an individual to develop the spectrum of atopic diseases. Most of these patients have a history of chronic relapsing eczematous skin disease dating from infancy which is treated with topical steroids as described by Küster.[3]

In 1952 Hogan[4,5] described five cases of atopic keratoconjunctivitis which he defined as a bilateral keratoconjunctivitis associated with atopic dermatitis, occurring at a variable interval after the onset of the eczema and showing a flare-up whenever the dermatitis worsened. As Foster pointed out in 1990, and our results corroborate his observation, some patients of this series had ocular inflammation which evolved independent of the dermatitis.[6]

Ocular complications are observed with a high frequency. In a study by Garrity and Liesegang that included 200 atopic patients 42·5% showed ocular problems such as blepharoconjunctivitis, cataracts, and corneal diseases.[4,6-8] We now report on a total of 50 patients who suffered both from atopic skin disease and different clinical forms of blepharitis.

Material and methods

Between January 1982 and December 1990 a total of 50 atopic patients (29 male, 21 female) presented at the outpatient clinic for infectious eye diseases with the signs of chronic inflammatory changes of the lids. This report describes the pertinent clinical, microbiological, and dermatological findings.

In ulcerative blepharitis the follicles of the lashes were involved, regularly being covered by thick matted, hardened crusts. Fibrin which exudes from the base of the skin defect usually masks the presence of the ulceration.[8] When carefully trying to remove these scales with a pair of forceps small, bleeding lesions in the area of the hair follicles appear regularly.

Squamous blepharitis was defined as a superficial and *non-destructive* inflammation of the lid margins with dry scaling being the prominent clinical feature in this subgroup. This type of lid involvement is considered to represent a localised eczematous dermatological disease.[9]

All patients were seen by the same dermatologist (KB-S). Their age ranged from 19 to 31 years (with a mean of 23·7 years). The duration of the blepharitis ranged from 5 to 36 months, with an average of 19·5 months.

All patients had a history of eczema dating from infancy sometimes combined with allergic rhinitis and asthma. Additional criteria for the dermatological diagnosis were the personal and family history of atopy (parents and first degree

Table 1 Microbiological results

	All patients (n=*50*) (*100%*)	*Patients with ulcerative blepharitis* (n=*21*) (*42%*)	*Patients with squamous blepharitis* (n=*29*) (*58%*)
Coagulase negative *Staphylococcus*	21	9	12
S aureus	38	16	22
Streptococcus (A & B)	15	7	8
Corynebacterium	18	10	8
Propionibacterium	21	12	9
E coli	4	2	2
Pseudomonas sp	4	3	1
Citrobacter	4	4	0
Candida species	19	19	0

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Accepted for publication
17 October 1991

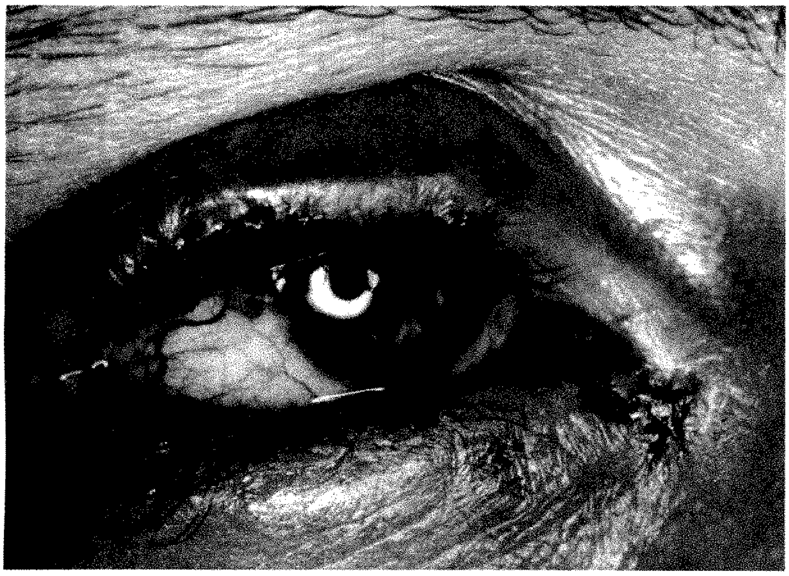

Figure 1 *Ulcerative blepharitis.*

relatives). The ocular diagnosis was based on the observation of a dermatitis of the lids, sometimes combined with meibomitis, trichiasis, distichiasis, and additional conjunctival and/or corneal signs such as giant papillae, follicles, or corneal scarring and neovascularisation.

Most of the patients had previously been treated unsuccessfully and had been referred for special work-up; 17 of our patients had additionally received topical steroids (12 had stopped this therapy weeks before our examination, five patients still used a corticosteroid ointment 3–6 times/day); both factors are known to contribute to fungal superinfection. Twenty one atopic patients underwent a laboratory examination including the total eosinophil count and quantitative immunoglobulins, such as IgE.

Separate samples for microbiological investigations (aerobic as well as anaerobic cultures) were harvested from all eyelids included in the study. To optimise recovery of micro-organisms the moistened sterile calcium alginate swab was passed along the anterior lid margin. For aerobic cultures different media (trypticase soy broth with 5% sheep erythrocytes, chocolate agar, manitol-salt agar, and endo agar) were used and incubated in a 5% CO_2 atmosphere for a minimum of 12 to 24 hours (if any growth was observed) and up to a maximum of 72 hours for the detection of anaerobic micro-organisms. For the culture of the latter Schaedler's broth gassed with an atmosphere of 97% CO_2 and 3% hydrogen (in GasPak Jars, BBL) was used. Fungi were cultivated on Sabouraud agar with and without inhibitors and specified by *Candida* API.

We determined the sensitivities to commonly given ophthalmic antibiotics and sulphonamides for all rapidly growing aerobic isolates by the Barry agar overlay method[10] using commercially available antimicrobial discs and Mueller Hinton agar (BBL). For *Propionibacterium acnes* the broth disc method of Wilkins and Thiel was employed.[11] No attempt was made to isolate *Pityrosporon ovale* or *Demodex folliculorum.*

Table 2 *Classification of* Candida *subtypes* (*n* = 19)

C albicans	13
C parapsilosis	4
C krusei	1
C stellatoidea	1

Results

An ulcerative blepharitis was observed in 21 (42%) of the patients (Fig 1). Frequent findings were dilated blood vessels on the inner lid margins (84%) and madarosis (56%): poliosis (6%) and trichiasis (4%) were less common. Squamous blepharitis was observed in 29 (58%) of our patients. We only found signs of a concomitant meibomitis in seven of the patients with this condition. The results of aerobic and anaerobic bacterial cultures from the lids are detailed in Table 1. Within the bacterial genus *Staphylococcus aureus* and coagulase negative *Staphylococcus (S epidermidis* and *S saprophyticus)* were the most frequently isolated organisms (38 (76%) cultures out of samples with positive cultures of *S aureus*, 21 (42%) cultures positive for coagulase negative *Staph*). The second most frequent isolates of the lids were *Corynebacterium* and *Propionibacterium*, which are considered to constitute normal inhabitants of the skin.

The culture for *Candida* species was positive in 19 samples (38%), the only affected patients being those with ulcerative blepharitis. In this group 19 of the 21 patients (90·4%) had fungal infections: *C albicans* in 13 cases, *C parapsilosis* four times, *C krusei* and *C stellatoidea* once (Table 2).

We were unable to isolate fungi from the patients with squamous blepharitis or from the conjunctival sac.

All patients with confirmed fungal infections received systemic therapy with two single doses of 100 mg ketoconazole per day and miconazole ointment topically six times a day for a duration of 6 weeks. In all cases repeated cultures after 6, 12, and 18 weeks were negative and the clinical findings considerably improved in all cases after this specific treatment. On discontinuation of therapy a relapse occurred in seven patients.

Only five of our patients (10%, four male, five female) showed severe ocular involvement. They all suffered from atopic keratoconjunctivitis as described by Foster: a chronic cicatrising conjunctivitis with serious corneal complications such as pannus formation in the superficial third of the peripheral cornea.[6] One patient had a history of eczema herpeticum of the face and some episodes of herpetic stromal keratitis.

Serum IgE levels (normally less than 100 IU/ml) were significantly elevated in 15 of the 21 patients tested (ranged from 205 to 610 IU, mean 345, SD 45). The serum IgE level of the other six patients was normal, although all of them had a history of eczema dating from infancy combined with allergic rhinitis or asthma. There was no correlation of the IgE level with the clinical picture of blepharitis or with the progress of disease observed.

Discussion

To the best of our knowledge this is the first report of a very high incidence (90·4%) of recovery of *Candida* species from the lid margins of atopic patients suffering from blepharitis of the *ulcerative* type.

Atopic patients are known to exhibit a defect in their cell-mediated immunity and possibly also a defective IgA antibody response.[3] These immunological changes may represent some of the contributing factors for the localised inflammatory changes of the lids which are caused by a variety of micro-organisms. On the other hand it cannot be overlooked that all of these patients had a long history of lid inflammation. It might well be that the presence of ulceration provides a suitable substrate for *Candida* to colonise.

We now postulate that only when *Candida* species happen to coincide with severe inflammation in atopic patients will a blepharitis of the ulcerative type develop or deteriorate, thereby implying that these micro-organisms may play an important role in the deterioration or development of this severe chronic inflammation.[9 12]

It is therefore advisable to perform repeated scrapings and cultures in every case of recalcitrant blepharitis. This is the only reliable way to rule out a frequent superinfection with fungi in ulcerative blepharitis and to provide specific and adequate treatment for this recalcitrant disease.[13 14]

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British Journal of Ophthalmology, 1992, 76, 275–279

Retinal blood flow alterations associated with scleral buckling and encircling procedures

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Abstract

The bidirectional laser Doppler technique and monochromatic photography were used to measure the absolute blood flow rate in the major temporal retinal arteries in seven patients following unilateral scleral buckling and encircling procedures, and in two patients before and after removal of scleral buckling elements. In the seven patients who had undergone uncomplicated scleral buckling procedures the arterial flow rates were on average 50% lower (p=0·01) in the surgically treated eyes than in the contralateral eyes. Removal of scleral buckling elements in two patients produced increases of 73% and 44% in arterial blood flow rates.

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Accepted for publication
17 October 1991

Ocular circulatory abnormalities have been associated with the repair of retinal detachment by scleral buckling and encircling procedures. Postoperative complications such as anterior segment[1-4] or posterior segment ischaemia,[5 6] or choroidal detachment,[7 8] following scleral buckling procedures while rare, are probably related to ocular circulatory abnormalities.

Experimentally it has been shown[9 10] that choroidal blood flow in the rabbit eye is reduced following scleral buckling procedures which involved the placement of encircling bands. The blood flow reduction was related to the degree of constriction of the band,[9] and when the encircling bands were removed the blood flow returned to normal.[10] Clinically Dobbie[11] found evidence for reduced choroidal blood flow in patients following scleral buckling procedures from his analysis of alterations of the ocular pulse wave.

In an initial study using the laser Doppler technique our group[12] reported that the pulsatile characteristics of the retinal arterial blood flow measured in eyes that had undergone uncomplicated scleral buckling procedures were altered compared with measurements obtained in fellow eyes. In addition a relative increase in retinal arterial blood flow was measured in one eye following removal of scleral buckling elements.

In the current study we used the newer bidirectional laser Doppler technique and monochromatic retinal photography to measure for the first time absolute retinal blood flow rates in seven patients who had undergone unilateral scleral buckling procedures for the repair of retinal detachment. Specifically we compared the blood flow rates measured in retinal arteries of surgically treated eyes with the flow rates measured in corresponding arteries in fellow eyes. In two additional patients who experienced complications after scleral buckling procedures absolute blood flow rates were measured in retinal arteries before and after removal of the buckling elements.

Patients and methods

Seven patients who had undergone uncomplicated unilateral scleral buckling and encircling procedures for quadrant or half-retinal rhegmatogenous retinal detachments were referred for laser Doppler measurements. Written informed consent was obtained from each patient. The entry criteria for the study were history of a unilateral scleral buckling procedure, no other known retinal vascular disease, visual acuity correctable to at least 20/70, adequate pupillary dilatation, and clear media. Characteristics of these patients and details of the surgical procedures are summarised in Table 1. The patients ranging in age from 20 to 47 years (mean 32 years) were referred for retinal blood flow measurements 13 to 89 months (mean 49 months) postoperatively. Refractive error ranged from 0 to −6·00 dioptres. Visual acuity was 20/30 or better in each eye. No other ocular or systemic disease was present. Duration of retinal detachment (mean 2·3 weeks) was estimated from the onset of symptoms described by the patients. In each case a no 276 or no 279 solid silicone intrascleral implant and a no 40 or no 240 encircling band were used in the buckling procedures. The extent of the intrascleral implant was 1·5 or 2·5 quadrants and was consistent with the size of the detachment. All patients were treated with diathermy in the bed of the scleral dissection. There were no ocular complications during surgery or postoperatively. In fellow eyes five patients had been treated with local cryotherapy around peripheral retinal holes. The other two patients had received no treatments in their fellow eyes.

Two additional patients were referred for retinal blood flow measurement before and after removal of scleral buckling elements. Written informed consent was also obtained from these patients. The first, a 38-year-old male, originally presented with a retinal detachment in his left

Table 1 Patient characteristics and surgical procedures

Patient	Age (years)	Sex	Eye treated	Postoperative period (months)	Detachment duration (weeks)	Implant extent (quadrants)	Implant/band
1	27	F	Left	88	2·0	1·5	276/40
2	28	F	Left	13	1·0	2	279/40
3	35	M	Left	52	1·0	2	279/240
4	47	M	Left	24	3·0	1·5	276/40
5	31	M	Left	15	0·3	2	276/40
6	33	F	Right	60	8·0	2·5	276/40
7	20	M	Right	89	1·0	1·5	276/40

Postoperative period=elapsed time between surgery and laser Doppler measurements.

eye. Ophthalmoscopic examination revealed a superotemporal quadrant retinal detachment with tears at the 11 o'clock position in the periphery. The right eye was normal. He underwent an uncomplicated scleral buckling procedure with cryotherapy around the tears. A no 276 solid silicone intrascleral implant was placed anti-clockwise from 1 o'clock to 8 o'clock. Diathermy was applied throughout the scleral bed. Subretinal fluid was drained. No encircling band was used. Sixteen months later the retina remained attached, visual acuity was 20/20, and intraocular pressure was 17 mm Hg. However slit-lamp examination revealed external redness over the buckle, a suture abscess, and extrusion of the implant. On the following day scleral buckling elements were removed without complications. Laser Doppler measurements were performed on the day before and 3 weeks following surgery.

The second, a 42-year-old male, originally presented with an inferonasal quadrant retinal detachment with a horseshoe tear at the 5 o'clock position in the right eye. Refractive error was −6·50 dioptres, visual acuity was 20/60, and intraocular pressure was 32 mm Hg. Treatment for elevated intraocular pressure was initiated. He underwent cryotherapy around the tear and a scleral buckling procedure. A no 279 silicone intrascleral implant was placed clockwise from 3.30 to 5.30 and a no 40 encircling band was then placed around the globe. Diathermy and drainage of subretinal fluid were not performed. Twenty nine months later a superonasal retinal detachment with a horseshoe tear at the 12.30 position was found. A second scleral buckling procedure, with cryotherapy around the new tear, was performed using a no 276 solid silicone intrascleral implant placed clockwise from 12.00 to 1.30 under the original encircling band. Eleven months after the second surgical repair ophthalmoscopic examination revealed transcleral intrusion of a bent encircling band at the 12 o'clock meridian. Thirty one months later the retina overlying the bent portion of the band was found to be eroded. In preparation for subsequent surgery the eroded region was surrounded by laser photocoagulation. Two months later the encircling band was cut and a 2 mm portion was removed without complications. Laser Doppler measurements were performed on the day before and 10 weeks following surgery.

LASER DOPPLER TECHNIQUE FOR RETINAL BLOOD FLOW MEASUREMENT

The principles of our application of the laser Doppler technique for measurement of blood velocity in retinal arteries have been described previously in detail.[13] With our technique the instantaneous centreline red blood cell velocity is determined from the spectral analysis of Doppler-shifted light scattered simultaneously in two directions (the so-called bidirectional technique). Prior to the retinal blood flow measurements pupils were dilated with 1% tropicamide. Monochromatic (575 nm) fundus photographs were taken of each eye. Intraocular pressure was measured by applanation tonometry and brachial artery blood pressure was measured by sphygmomanometry.

During data acquisition patients were positioned before a slit-lamp apparatus equipped with a helium-neon laser light source ($\lambda=633$ nm) and detector assembly consisting of two photomultiplier tubes. The signals from the photomultiplier tubes were recorded simultaneously on two tracks of a Honeywell 5600C Recorder/Reproducer for approximately 1 minute at each measurement site. A pulse synchronous with the heart rate was recorded on a third track using a transducer attached to the patient's fingertip.

For data analysis a frequency tracking system was used to identify portions of the recorded photocurrent showing regular systolic-diastolic variations in the Doppler-shift frequency. These portions were recorded when the incident beam was well-centred on the retinal artery. Spectral analysis of the identified portions of the recorded photocurrent was carried out under computer control. A Hewlett-Packard HP 9816S instrumentation-controlling computer was interfaced with two Wavetek 5809 digital spectrum analysers. Pairs of Doppler-shift spectra were obtained throughout the cardiac cycle and displayed on two Electrohome video monitors. Each spectrum exhibited large fluctuations in spectral power up to a clearly measurable maximum frequency shift corresponding to the velocity of the red blood cells flowing at the centreline of the artery. The spectrum and the maximum frequency shift was then read out onto a Hewlett-Packard HP 7470A digital graphics plotter.

The time average of the centreline blood velocity during the cardiac cycle ($\bar{V}$) was determined using the previously established relationship[13]:

$\bar{V}=V$ (diastole)$+k$ [V(systole)$-V$(diastole)] where $k=0{\cdot}48$ (SD 0·04). The blood flow rate was calculated as

Flow$=\bar{V}\times$area/2

where area is the cross-sectional area of the retinal artery at the laser Doppler measurement site.[14] The area was calculated from the measured blood column diameter assuming a circular cross-section. The blood column diameter was measured from monochromatic (575 nm) retinal photographs using an instrument calibrated to produce readings in μm from a magnified retinal image.[15]

As previously described[14] the uncertainty associated with individual measurements of the centreline blood velocity in retinal arteries is approximately plus or minus 20%. The uncertainty associated with arterial diameter measurements is approximately plus or minus 2%.[15]

Data were analysed using the paired Student's *t* test or correlation analysis. A p value of 0·05 or less was considered statistically significant.

Results

Table 2 shows the results of the laser Doppler measurements as well as the intraocular pressures measured in both eyes of the seven patients who had previously undergone uncomplicated

Table 2 Intraocular pressure and laser Doppler measurements

	Intraocular pressure (mm Hg)			*Diameter (μm)*			*Centreline blood velocity (cm/s)*			*Blood flow rate (μl/min)*		
Patient	*Tx*	*Fellow*	*% Diff*	*Tx*	*Fellow*	*% Diff*	*Tx*	*Fellow*	*% Diff*	*Tx*	*Fellow*	*% Diff*
1	16	19	−16	118	122	−3	3·5	5·2	−33	11·5	18·2	−37
2	15	20	−25	95	129	−26	2·6	7·3	−64	5·5	28·6	−81
3	17	18	−6	119	127	−6	3·7	6·7	−45	12·3	25·5	−52
4	13	14	−7	124	113	10	2·9	4·0	−27	10·5	12·0	−12
5	15	21	−29	106	105	1	2·8	4·5	−38	7·4	11·7	−37
6	11	14	−21	98	104	−6	1·2	3·3	−64	2·7	8·4	−68
7	16	19	−16	111	136	−18	2·5	4·4	−43	7·3	19·2	−62
Mean (SD)			−17 (9) p=0·004*			−7 (12) ns*			−45 (14) p=0·002*			−50 (23) p=0·01*

*Comparison between treated and fellow eyes (2-tailed paired *t* test).
Tx=surgically treated eye; Fellow=fellow eye; % Diff=difference between treated and fellow eyes; ns=not significant.

unilateral scleral buckling procedures for rhegmatogenous retinal detachment (Table 1). In each case intraocular pressure was lower in the surgically-treated eye than in the fellow eye. The average percentage difference, 17 (SD 9)% was statistically significant (p=0·004).

Laser Doppler measurements were obtained from a major superior or inferior temporal retinal artery in each surgically-treated eye and from the corresponding artery in the fellow eye. The retinal arteries were narrower in treated eyes in five of the seven patients but the average percentage difference, 7 (SD 12)%, was not statistically significant. However centreline blood velocity was markedly lower in each treated eye artery than in the corresponding fellow eye artery. The average percentage difference, 45 (SD 14)%, was statistically significant (p=0·002). The pulsatility ratio, defined as the ratio of the centreline blood velocity measured at systole to that measured at diastole, was also computed for each artery. In each case this ratio was lower for arteries in treated eyes than in fellow eyes.

The arterial blood flow rate in each treated eye was lower than in the fellow eye due primarily to the marked differences in blood velocity rather than to the small differences in measured arterial diameter. The average percentage difference in blood flow rate, 50 (SD 23)%, was statistically significant (p=0·01).

Correlation analysis was used to determine if the results of the laser Doppler measurements were related to details of the prior surgery (duration and extent of the retinal detachment, elapsed time between surgery and measurements, extent of the implant, and presence or absence of fellow eye treatment) or to difference in mean blood pressure, heart rate, refractive error, or intraocular pressure. Only one significant correlation was found. As shown in Figure 1 there was a significant (r=0·82, p=0·02) linear relationship between the centreline blood velocity and the intraocular pressure measured in surgically treated eyes. An interpretation of this finding is presented below.

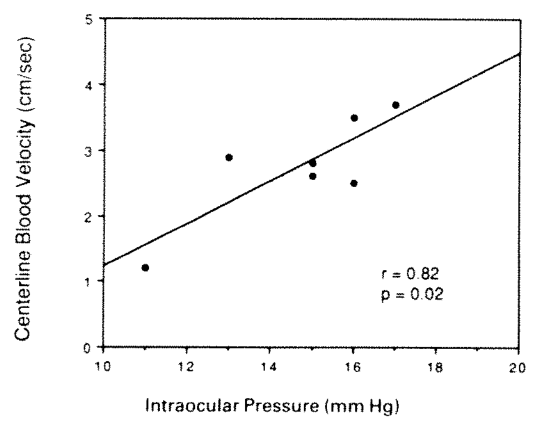

Figure 1 Centreline blood velocity measured in retinal arteries of surgically treated eyes of patients who had undergone scleral buckling procedures plotted as a function of the intraocular pressure.

Monochromatic retinal photographs of the two patients who were studied prior to and following surgical removal of scleral buckling elements are shown in Figures 2 and 3. The photographs shown were taken at the time of the laser Doppler measurements which followed removal of the buckling elements.

In the eye shown in Figure 2 prior to the removal of the intrascleral implant the diameter of the superotemporal artery at the laser Doppler measurement site was 126 μm, the centreline blood velocity was 2·9 cm/s, and the blood flow rate was 11 μl/min. Following surgery the measured arterial diameter was 122 μm, the centreline blood velocity increased to 5·5 cm/s, and the blood flow rate increased by 73% to 19 μl/min.

In the eye shown in Figure 3 prior to the removal of a portion of the encircling band the diameter of the superotemporal artery at the laser Doppler measurement site was 117 μm, the centreline blood velocity was 2·6 cm/s, and the blood flow rate was 9 μl/min. Following surgery the measured arterial diameter was 127 μm, the centreline blood velocity increased to 3·5 cm/s, and the blood flow rate increased by 44% to 13 μl/min.

In both of these patients the increases in arterial blood flow rate following surgery were due primarily to the increases in blood velocity.

Discussion

Our finding that the blood flow rates in retinal arteries of eyes that had undergone scleral buckling and encircling surgery were on average 50% lower than the flow rates measured in corresponding arteries in fellow eyes results from two factors: differences in vessel diameter and differences in blood speed. On average vessel diameters were 7% smaller in treated eyes than in fellow eyes. We have previously shown[14] that the blood speed varies as the square of the vessel diameter in the major branch retinal arteries of healthy volunteer subjects. Thus a 7% difference in vessel diameter would normally be accompanied by a 14% to 15% difference in blood speed. In the treated eyes however the

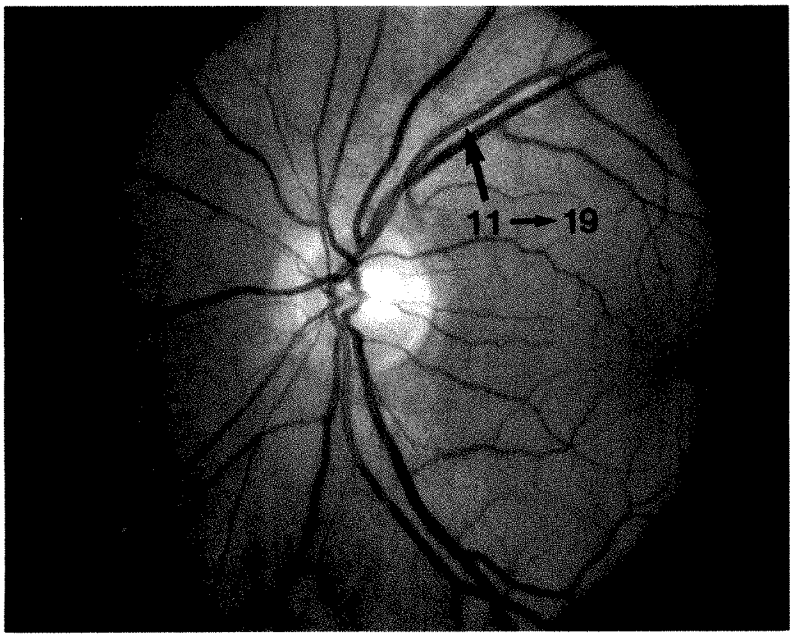

Figure 2 Photograph of the left eye of a patient taken after removal of an intrascleral implant. Blood flow rates (μl/min) measured before and after surgery are shown. Large arrow indicates the measurement site.

blood speed was, on average, 45% lower than in fellow eyes. The measured difference in blood speed is thus much greater than would be expected due to differences in vessel diameter alone.

It is likely that the reduced blood speed is due to compressional mechanisms acting on the retinal vasculature. Ohkubo[16] found signs of reduced retinal perfusion in regions of reattached retina which were indented following scleral buckling procedures. Compressional mechanisms have been cited as the cause of reduced choroidal blood flow following scleral buckling procedures.[9-11] In the case of the choroidal circulation reduced blood flow was attributed to the direct obstruction of choroidal venous drainage. Clearly however there is no direct compression of the central retinal vein due to scleral buckling or encirclement. Compression of the peripheral retinal circulation due to indentation is thus the likely cause of the reduced retinal blood flow rate.

Our finding of a significant positive correlation between retinal blood speed and intraocular pressure in treated eyes provides indirect evidence that there is a parallel reduction in retinal and choroidal perfusion following surgery. As described by Dobbie[11] there is altered perfusion of the anterior choroid, ciliary body, and ciliary processes in patients with encircling bands. This altered perfusion results in a decreased ocular pulse amplitude, decreased aqueous humour formation and, as a result, a chronically decreased intraocular pressure. We also found that intraocular pressure was lower in surgically treated eyes than in fellow eyes. If we associate a lower intraocular pressure with a lower choroidal perfusion then our finding of a positive correlation between retinal blood speed and intraocular pressure suggests that the largest reductions in retinal blood speed occur when the choroidal perfusion is also most impaired.

Our finding of marked increases in retinal arterial blood flow following removal of scleral buckling elements in two patients confirms our previous report[12] of a similar increase measured in a patient following removal of an intrascleral implant and an encircling band. As cited above Diddie and Ernest[10] found that removal of encircling bands in rabbit eyes returned the decreased choroidal blood flow to normal levels. Removal of buckling elements thus appears to affect both the choroidal and retinal circulations in a similar manner.

It should be stressed that even though retinal and choroidal blood flow decreases appear to be a common occurrence after scleral buckling procedures patients do not typically experience long term visual complications following successful surgery. In cases where there are complications it may be due to the fact that in those patients there is a greater susceptibility to the effects of reduced ocular blood flow.

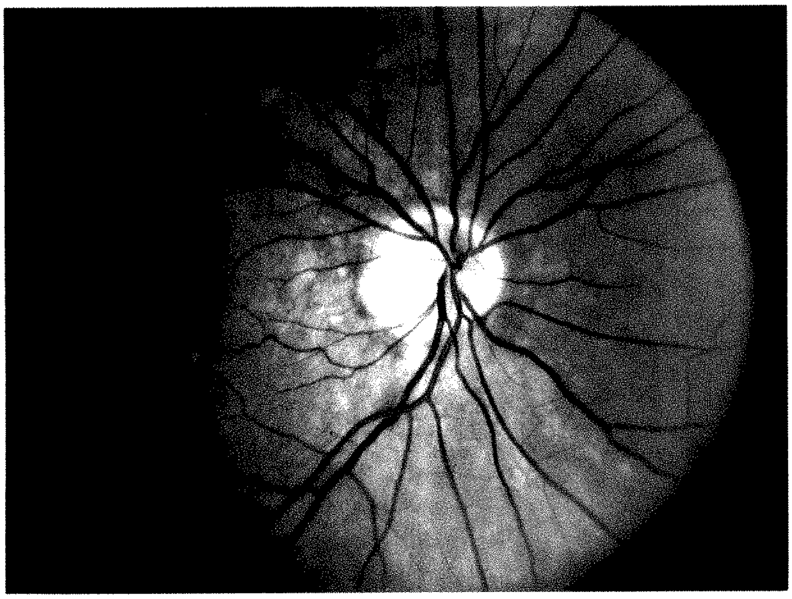

Figure 3 Photograph of the right eye of a patient taken after removal of a portion of an encircling band. Blood flow rates (μl/min) measured before and after surgery are shown. Large arrow indicates the measurement site.

This work was supported in part by USPH Grant EY01303 from the National Institute of Health and the Massachusetts Lions Eye Research Fund.

The authors wish to thank Douglas G Goger, BA for his assistance in analysing the data and for his helpful comments. We also thank Charles L Schepens, MD and Ronald C Pruett, MD for referring patients for this study.

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British Journal of Ophthalmology, 1992, 76, 280–283

Diurnal intraocular pressure variations: an analysis of 690 diurnal curves

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Abstract

Out of a total of 2272 diurnal curves (DC) of intraocular pressure (IOP) obtained from 1178 patients 690 first curves of the right eye of all patients were analysed. For each DC there were 4–6 IOP readings taken between 8 am and 6.30 pm of the same day. The patients' diagnosis, age, sex, type of IOP lowering medication, diabetes, and the calendar month of the year were recorded. In 40% of cases the highest IOP was found at the earliest morning measurement with some 65% of peaks occurring before noon. The lowest IOP measurement showed no specific predilection for any particular time of the day. These findings were true for all diagnosis groups. The mean range of IOP fluctuation during the DC was 5·0 mm Hg in normals, 5·8 mm Hg in patients with open angle glaucoma (OAG), and 6·8 mm Hg in patients with ocular hypertension (OHT). Patients treated with timolol had a lower mean IOP fluctuation range than those on other types of IOP lowering treatment. No association was found between all other parameters examined and the diurnal IOP distribution.

Intraocular pressure (IOP) is subject to chronobiological rhythms similar to other physiological values in the human body. IOP measurements during different hours of the day have a well recognised clinical importance which can directly affect the diagnosis and management of the patient with IOP related conditions.

In clinical practice performing diurnal IOP curves (DC) has several indications: (1) in patients with ocular hypertension (OHT) it is essential to obtain baseline IOP levels and monitor the condition, (2) in glaucomatous patients with progressive damage whenever single IOP measurements are within the 'normal' range, and (3) in cases when a suspicious looking optic disc is discovered in patients without apparent IOP elevation.

The information offered to the attending ophthalmologist by the DC (or 'phasing' as some prefer to call it) as opposed to the single IOP reading is manifold:

(1) it gives a better indication of the IOP levels since the solitary reading taken in the office may not reveal the peak IOP level;

(2) it identifies the time of the day when the peak IOP occurs;

(3) it clarifies the range of IOP fluctuation during the examination period.

Each of these answers provides valuable data which will ensure better understanding and management of the individual's disease process.

For these reasons the performing of diurnal IOP examinations has been widely practised in glaucoma clinics for many years and the literature is abundant with information on the subject. There is general agreement with respect to the range of IOP fluctuation. It has been shown that this does not usually exceed 3–6 mm Hg in normal eyes[1 2] but can reach 10 mm Hg and more in glaucoma patients before initiating treatment.[1–4]

There are conflicting reports in the literature however as to the time of the day at which the peak IOP occurs during the DC. Some reports found the peak IOP in the morning,[2 5] while others have shown that it may occur at any time during the day.[3 6] All these studies have several drawbacks: they were performed mostly on patients in hospital, the majority employed the Schiotz tonometer for measuring IOP and the number of eyes studied varied from 20 to 500.

The objective of this study is to evaluate the distribution of IOP levels during the day – during those hours that it is customary to examine ambulatory patients – and its association with several parameters including diagnosis, type of treatment, and demographic characteristics.

Clinical material

The Glaucoma Clinic of the Soroka University Hospital is a central referral service for the Sick Fund Health Insurance covering some 90% of a population of more than 300 000 people. All persons who need a DC evaluation are referred to this clinic. DCs are performed on most new referrals and whenever indicated in the case management. Untreated ocular hypertensives have a DC examination every other year.

The present study is based on the information collected from the DCs performed at the Glaucoma Clinic under similar conditions between 1979 and 1989.

Patients scheduled for DC examination were invited to the outpatient clinic at 7.45 am for IOP testing every 2 hours until at least 6 pm. At the time the appointment for the DC was given the patients were instructed to take their morning

Table 1 Timetable for six IOP measurements during the diurnal curve

Time of reading
1 early morning (7.45 am until 9.00 am)
2 mid-morning (9.45 am until 11.30 am)
3 mid-day (11.30 am until 2.00 pm)
4 early afternoon (2.00 pm until 4.00 pm)
5 mid-afternoon (4.00 pm until 5.30 pm)
6 evening (5.30 pm until 7.00 pm)

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Accepted for publication
17 October 1991

Table 2 Number of IOP measurements on each diurnal curve

	n	(%)
Six readings	873	(38·4)
Five readings	1209	(53·2)
Four readings	190	(8·4)
Total diurnal curves	2272	

medication(s) and to bring them along on the day of their appointment. Patients arriving for the DC after 9 am were not examined but given a new appointment.

There were six scheduled IOP readings for the DC as shown in Table 1.

The first four IOP measurements were taken in the outpatient clinic, usually by the resident on duty for the following 24 hours who was also taking the last two IOP measurements for the DC in the inpatient ward. All IOP measurements were performed with the Goldman applanation tonometer attached to the slit-lamp.

All DCs were recorded on a chart covered with millimetric paper, with the hours of the day marked on the abscissa and the IOP on the ordinate. Each chart accommodates both eyes and it bears the patient's name, ID number, and the date of the DC. After completing the DC the charts were reviewed by a glaucoma subspecialist and consequently returned to the glaucoma file for safekeeping.

For the purpose of the present study all glaucoma files were reviewed and the following data were recorded if a DC was present:

(1) demographic information: age, sex, date of DC

(2) for diabetic patients, whether insulin treated or not

(3) the patient's diagnosis in the glaucoma clinic

(4) the IOP and the time of each measurement

(5) the type of treatment the patient was receiving; four categories of treatments were recorded:

(i) no treatment

(ii) topical β blocker alone

(iii) topical β blockers and other IOP lowering drugs

(iv) any IOP lowering medication(s) except β blocker. The β blocker used throughout the study period was timolol.

Under the diagnosis 'aphakic/pseudophakic' were included patients who had no increased IOP before their cataract surgery. For patients with more than one DC in the file each curve was recorded.

Patients who completed at least four IOP measurements on their DC were included in the study. The results are presented in terms of patients, using the findings of the right eyes only, after ascertaining that the results were similar in both eyes.

Unless otherwise stated the first DC of each patient was used in each analysis so that each curve can be considered an independent event. If more than one curve for each patient had been included then persons with more than one curve would be disproportionately represented in the analyses.

Associations and statistical significance were calculated using the t test, analysis of variance, and χ^2 methods.

Results

The review of more than 1400 glaucoma files in the clinic identified 1178 persons who had completed 2272 diurnal curves; 650 (55%) were men and 528 (45%) were women. The mean age of persons in the study excluding those with a diagnosis of developmental glaucoma was 62·2 (SD 12·1) years.

Of the 2272 DCs 38·4% had completed all six pressure measurements and 53·2% had five IOP values. Only 8·4% had four measurements (Table 2).

The number of DCs for each individual is shown in Table 3.

Table 4 displays the distribution of the DCs by diagnosis for each eye separately. The DCs diagnosed as 'other' included developmental, secondary, traumatic, and low tension glaucoma. Since the number of cases in each of these subgroups is small they were not included in the analysis of the results by diagnosis. After excluding these cases 690 first DCs of right eyes were left for analysis.

In Table 5 the distribution of the peak IOP reading in the various diagnostic groups at the six different time checks is presented for the 690 DCs. Overall 41% of peaks were found on the first, earliest IOP measurement, in the morning and another 24% at the second, mid-morning examination, while only 2% exhibited the peak IOP in the last, evening IOP reading. This trend remained consistent in each diagnostic group. These results are presented graphically in Figure 1.

Contrary to the peaks which showed the clear tendency to present in the morning hours the lowest IOP values were scattered at all times of the day regardless of the diagnostic groups (see Table 6 and Fig 2). This pattern of peaks and troughs was also found when the 259 patients with two curves and the 90 patients with three curves were evaluated separately.

The mean IOP was found to be highest in the morning hours with a steady decline throughout the day. This trend was consistent in each diagnostic group and is presented in Figure 3.

The mean range of IOP fluctuation (highest

Table 3 Number of patients, eyes, and diurnal curves

Number of DCs	*Patients (n)*	*Eyes (n)*
1	767	1483
2	269	517
3	90	171
4 or more	52	101
Total DCs	1178	2272

Table 4 Number of diurnal curves by diagnosis

	Total	*Right eye*	*Left eye*
Normal	206	100	106
Open angle glaucoma (OAG)	482	250	232
Ocular hypertension (OHT)	1094	533	561
Chronic angle closure (CACG)	253	127	126
Aphakic/pseudophakic	92	51	41
Other	145	77	68
Total	2272	1138	1134

Table 5 Distribution of IOP peaks by time of the day and diagnosis

	Time of reading						
	1	*2*	*3*	*4*	*5*	*6*	
Diagnosis	%	%	%	%	%	%	(*n*)
Normal	40·5	22·6	19·0	6·0	9·5	2·4	(84)
OAG	37·9	24·3	12·9	12·9	10·0	2·1	(140)
OHT	45·7	24·0	11·7	9·1	7·1	2·3	(350)
CACG	32·5	26·3	10·0	11·3	17·5	2·5	(80)
Aphakic/pseudophakic	35·1	18·9	18·9	13·5	8·1	5·4	(36)
Total	41·4	23·9	13·0	10·0	9·3	2·4	(690)

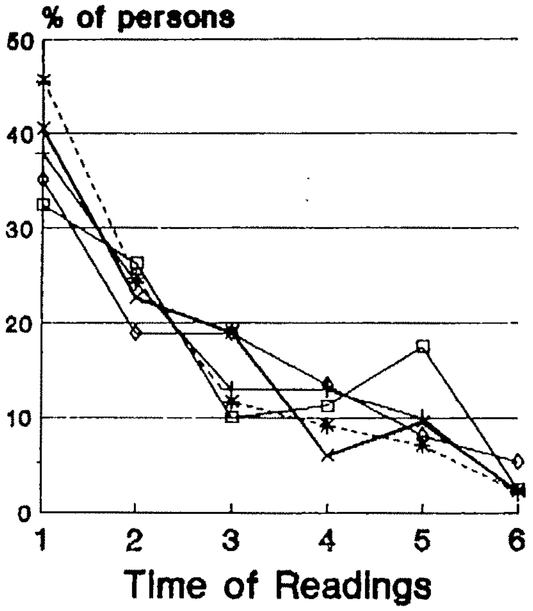

Figure 1 Distribution of peaks by diagnosis and time of readings. Time of readings: (1) 7.45 am until 9.00 am; (2) 9.45 am until 11.30 am; (3) 11.30 am until 2.00 pm; (4) 2.00 pm until 4.00 pm; (5) 4.00 pm until 5.30 pm; (6) 5.30 pm until 7.00 pm. (×) normal, (+) OAG, (*) OHT, (□) CACG, (◊) aphakic/pseudophakic.

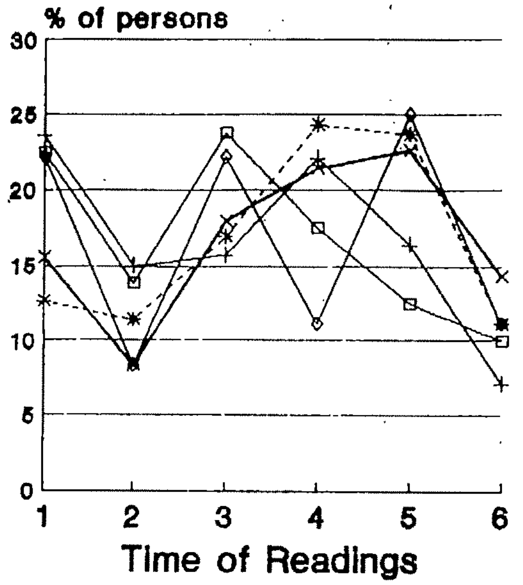

Figure 2 Distribution of troughs by diagnosis and time of readings. Time of readings: (1) 7.45 am until 9.00 am; (2) 9.45 am until 11.30 am; (3) 11.30 am until 2.00 pm; (4) 2.00 pm until 4.00 pm; (5) 4.00 pm until 5.30 pm; (6) 5.30 pm until 7.00 pm. (×) normal, (+) OAG, (*) OHT, (□) CACG, (◊) aphakic/pseudophakic.

Table 6 Distribution of IOP troughs by time and diagnosis

	Time of reading						
	1	*2*	*3*	*4*	*5*	*6*	
Diagnosis	%	%	%	%	%	%	(*n*)
Normal	15·5	8·3	17·9	21·4	22·6	14·3	(84)
OAG	23·6	15·0	15·7	22·1	16·4	7·1	(140)
OHT	12·6	11·4	16·9	24·3	23·7	11·1	(350)
CACG	22·5	13·8	23·8	17·5	12·5	10·0	(80)
Aphakic/pseudophakic	22·2	8·3	22·2	11·1	25·0	11·1	(36)
Total	16·8	11·8	17·8	22·0	20·9	10·6	(690)

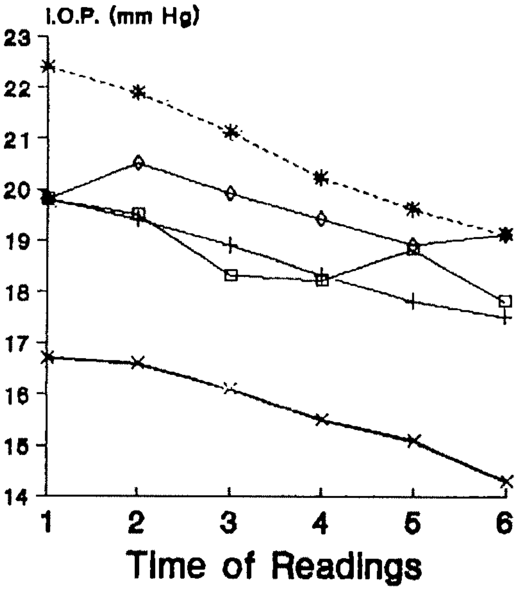

Figure 3 Mean IOP by diagnosis and time of readings. Time of readings: (1) 7.45 am until 9.00 am; (2) 9.45 am until 11.30 am; (3) 11.30 am until 2.00 pm; (4) 2.00 pm until 4.00 pm; (5) 4.00 pm until 5.30 pm; (6) 5.30 pm until 7.00 pm. (×) normal, (+) OAG, (*) OHT, (□) CACG, (◊) aphakic/pseudophakic.

minus lowest IOP) during the DC is shown in Table 7. While the mean IOP range for normals was 5·0 mm Hg it was 5·8 mm Hg for OAG and CACG and 6·8 mm Hg for OHT. These differences were found to be statistically significant ($p<0·001$).

The type of treatment the patients were receiving at the time of the DC was not associated with the distribution of peaks and troughs. It was however associated with the range of diurnal IOP fluctuation as expressed by the mean range of IOP: patients on β blockers had a lower mean IOP range than those on other types of medication (Table 8). This small difference reached statistical significance ($p=0·019$).

Analysis of the patients' age, sex, the presence and type of diabetes (insulin treated vs non-insulin treated), and the season of the year (warm – May through October vs cold – November through April), had no effect on any of the parameters examined: time of peak, time of trough, and range of IOP.

Table 7 Mean of IOP fluctuation by diagnosis groups

Diagnosis	*mm Hg*	*SD*	*n*
Normal	5·0	2·7	84
OAG	5·8	2·9	140
OHT	6·8	3·2	350
CACG	5·9	3·4	88
Aphakic/pseudophakic	5·8	2·9	37

$F=7·03$; $p<0·001$.

Table 8 IOP range of fluctuation by type of treatment (all diagnoses)

	IOP mm Hg	
Type of treatment	*Mean*	*SD*
No treatment	6·2	2·7
β blocker only	5·5	2·6
β blocker plus other	5·5	2·7
Other except β blocker	6·3	3·4

ANOVA $F=3·4$; $p<0·019$.

Discussion

Identifying the peak IOP in each individual's follow-up is the main reason for conducting DCs. Worthen[7] reviewed the literature and found that both in normals and glaucomatous eyes the peak IOP occurred before 2.00 pm. Such a pattern was also found in a glaucoma screening programme scheduled for mornings and afternoons: the morning screening yielded 17% elevated IOP while the afternoon only 9%. Furthermore re-examination of the IOP in the afternoon after the morning reading showed higher values in only 10% of cases but lower values in 51%.[8]

As stated earlier most of the studies quoted suffered from several limitations and possibly for that reason there is the continued practice of performing diurnal pressure curves, often with patients entering hospital for this purpose.

There are several advantages to our study. The first is that it included all persons who had a diurnal curve recorded in their glaucoma file and did not include a selected population. We have no reason to think that this population differs from others in need of DC evaluation. Second, the DC evaluation was conducted in an outpatient setting with minimal interference with the patients' life style and treatment regimen. In addition the IOP measurements were conducted using the modern standards generally accepted today in glaucoma practice.

We realise that starting the DC in the clinic around 8 am is less than ideal: there are reports claiming the highest IOP occurs immediately after waking.[9] It is also possible that the home tonometry, as advocated by Zeimer,[10] covers a larger portion of the 24 hour cycle. Nevertheless the widely employed practice today is IOP measurement by ophthalmologists in their offices, and therefore the information collected and presented here is still useful.

The clinical importance of our finding, that two thirds of the peak IOPs occur before noon and only 30% during the following 7 hours in this large series, raises a serious question as to the necessity of extending the DC hours beyond 4.00 pm. More important it emphasises the fact that solitary IOP examination taken in the late afternoon or early evening may miss up to 97% of IOP peaks! Bearing in mind that some glaucoma clinics are held in the afternoon and in many private practices the patients prefer the late appointments (after business hours, traffic rush, etc), this finding indicates that a revision of the timetable for IOP examination in the glaucoma population may be warranted.

The range of IOP fluctuation during the DCs in the various diagnostic groups is slightly different from those reported in earlier studies. The range of fluctuations we found in patients with various types of glaucoma was smaller than in ocular hypertensives. One of the reasons for this finding is that all glaucoma patients seen at the glaucoma clinic are referrals from ophthalmologists in the general eye clinics where medication is started immediately at time of the diagnosis. On the other hand many of the ocular hypertensives are followed carefully but left untreated. Out of 360 first (RE) DCs performed on ocular hypertensives only 21% were on treatment. The range of fluctuation among those not treated was only slightly higher than those treated (6·8 mm Hg versus 6·5 mm Hg respectively).

The finding that topical β blockers flatten the diurnal IOP curve has been reported before in studies using timolol[11,12] and both timolol and levobunolol[13] on smaller groups of patients; in the present study of DCs of the 273 treated patients 40·6% were receiving timolol (alone or in combination with other IOP lowering drugs) and 59·4% were on medication(s) other than β blockers. Due to the large number of cases the small (1 mm Hg) difference between the mean IOP in the subgroups reached statistical significance. However the clinical importance of this finding is questionable.

We did not find associations between age, sex, the presence of diabetes, and the IOP parameters examined (time of peak, trough, and daily fluctuation). Moreover examination of the 411 patients with multiple DCs throughout the year did not detect any seasonal variations in the pattern of their IOP behaviour.

This paper has been partly presented at the Association for Research in Vision and Ophthalmology meeting, Sarasota, FL, May 1990.

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British Journal of Ophthalmology, 1992, 76, 284–288

Onset of retinopathy of prematurity as related to postnatal and postconceptional age

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Abstract

The hypothesis that both perinatal events and stage of retinal development are important factors in determining the age at onset of retinopathy of prematurity (ROP) was tested by comparing gestational age at birth with postnatal and postconceptional age when ROP (using ICROP) was first seen. The study population consisted of 207 infants (111 placebo (P) treated, 96 vitamin E (E) treated) who developed ROP among a group of 914 premature infants (460 P, 454 E) enrolled in a randomised clinical trial of the effect of prophylactic use of vitamin E at pharmacological serum levels on incidence and severity of retinopathy. The mean postnatal age at onset of retinopathy was delayed in E treated infants compared with P treated infants by 1·4 weeks ($t=4{\cdot}004$, $p<0{\cdot}0001$). For both P and E treated infants postnatal age at onset of ROP (which reflects the state of retinal development at which birth insults occur) and postconceptional age at onset of ROP which defines state of maturity) were correlated with gestational age at birth. This suggests that both the event of premature birth and the extent of retinal development are important in determining when ROP will first be observed.

In this report the relationship of the postnatal age when retinopathy of prematurity (ROP) was first observed is compared with postconceptional age at first observation of ROP for infants born between 26 and 35 weeks of gestation. This observation provides insight into factors controlling initiation of abnormal vascularisation in the immature retina which characterises ROP. We also report the influence of the antioxidant vitamin E (E) on the onset of ROP. The data that permit this analysis are derived from a group of 914 infants with birth weights (BW) of less than 2001 g or less than 37 weeks gestational age (GA) who were enrolled in a double blind, randomised clinical trial designed to evaluate the prophylactic use of E at pharmacological serum levels (5 mg/ml) in decreasing incidence and severity of ROP. Infants were treated prophylactically with either placebo (P) or E.

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Accepted for publication
17 October 1991

Materials and methods

SUBJECTS AND STUDY MEDICATION ADMINISTRATION

The study was undertaken at the Neonatal Complex of the University of Pennsylvania which includes the Infant Intensive Care Nurseries at Pennsylvania Hospital, The Hospital of the University of Pennsylvania and The Children's Hospital of Philadelphia, the latter serving an entirely outborn population. Enrolment began on 1 January 1979 and ended 1 May 1981. Informed consent and enrolment were accomplished as soon as possible after birth but infants were eligible up to 5 days of age. Once enrolled infants were randomly assigned to a study number and the corresponding study medication (placebo or vitamin E) within five BW strata: $\leq$1000 g, 1001–1250 g, 1251–1500 g, 1501–2000 g, and $\geq$2000 g if $\leq$36 weeks GA and requiring >23 hours of oxygen. Details regarding randomisation, method of study medication administration, laboratory analyses undertaken, the clinical data base recorded for each patient, and reasons for lack of follow-up are available in previous reports.[1,2]

CLASSIFICATION AND SURVEILLANCE OF ROP

ROP was characterised in this study using a classification system developed at the University of Pennsylvania[3,4] prior to the cooperative efforts that led to the International Classification of ROP (ICROP).[5,6] The former classification corresponds closely to ICROP. For the sake of clarity the conclusions presented in this report have been based on the widely used ICROP classification. The Schaffer-Quinn classification system defines vascular abnormalities characteristically seen in the earliest stage of ROP as also described by Patz[6] and McCormick.[7] These changes which are more difficult to define and standardise were not included in the ICROP classification. The demarcation line that characterises stage 1 ICROP corresponds to grade 2 in the Schaffer-Quinn classification. Stages 3, 4, and 5 are identical.

ROP surveillance began as soon as the neonatologist in charge felt that the infant could tolerate the procedure, usually in the first week of life and often in the first day or two of life Surveillance for retinopathy included weekly eye examinations which continued throughout the period of retinal vasculature immaturity or until any ROP observed had begun to regress or progressed to retinal detachment. Ophthalmic follow-up continued to age 3 years.

All examinations were carried out by one of

Table 1 Characteristics of study population

	Birth weight (g) (SD)	*Gestational age (weeks) (SD)*
All placebo enrollees (*n*=460)	1444 g (439)	31·6 (2·8)
All vit E enrollees (*n*=454)	1461 g (457)	31·5 (2·7)
Placebo infants with ROP (*n*=111)	1149 g (295)	29·8 (2·3)
Vit E infants with ROP (*n*=96)	1092 g (212)	29·4 (2·0)

two ophthalmologists. The examiners had undergone extensive interobserver reliability testing and maintained interobserver agreement at 95% for the early vascular changes of ROP and 99% for stage 1 ICROP or worse disease.[8] In addition, for quality control, a retinal consultant examined 10% of study infants to corroborate findings.

STATISTICAL METHODS

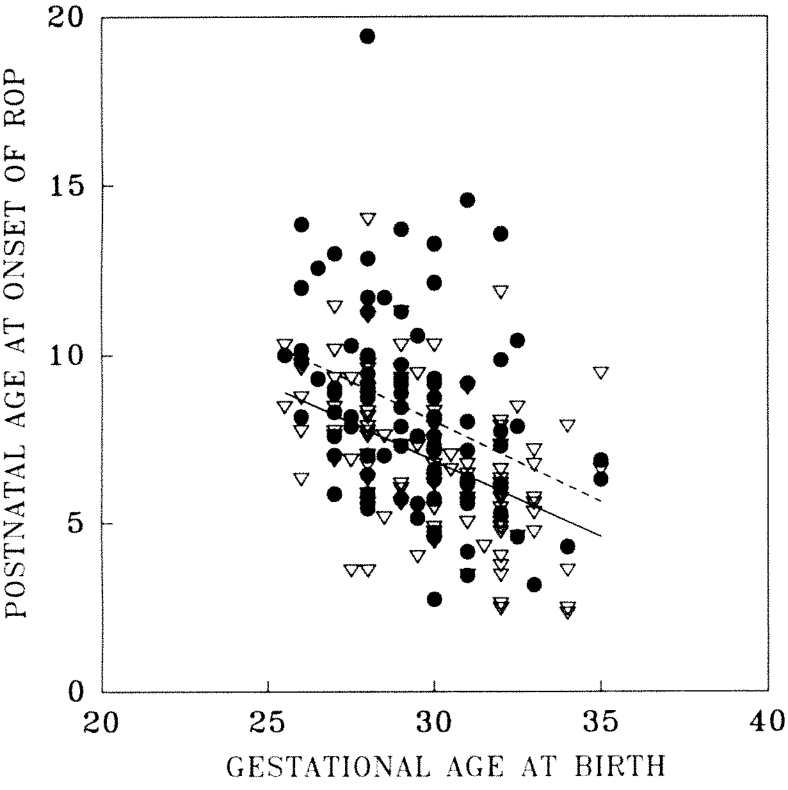
Onset of ROP was defined as the time when ROP was first observed clinically. Unless otherwise stated onset of ROP was defined as onset of stage 1 ICROP. When onset is defined as the earliest vascular abnormalities defined in the Schaffer-Quinn classification it is clearly stated. The analysis was performed for right and left eye of study infants.

Analysis was undertaken by considering the following variables: BW, GA at birth (as determined on enrolment by physical assessment and maternal history), and age at onset of ROP. Unpaired *t* tests, two tailed, were performed with significance defined as $p=0\cdot05$ or less.

Results

Nine hundred and fourteen infants were enrolled and complete acute phase ROP information was collected on 755 children (385 P and 370 E). Of these 424 had BW $\leq$1500 g (216 P, 208 E). Among P treated infants, 111 developed Stage 1 ICROP or worse in one or both eyes (110 OD, 108 OS). For E treated infants, ROP developed in one or both eyes of 96 infants (94 OD, 93 OS). ROP was therefore unilateral in nine infants (4 P, 5 E), occurring only in the right eye five times and only in the left eye four times. Right eye data are the subject of this report, however, results of the analysis are not different and no significant changes are noted if the analysis is done with the left eye data point.

Figure 1 The postnatal age (weeks) at onset of ROP compared with the GA at birth for the 111 P treated infants (▽) and 96 E treated infants (●) who developed ROP. The best fit regression line for P treated infants is represented by the solid line (slope −0·47) and for the E treated group by a broken line (slope −0·48).



Previous reports of this trial[1,2] employed the Schaffer-Quinn classification and included the 13 P treated and three E treated infants who developed ROP not severe enough to be characterised as ROP in the ICROP classification. These infants are not included in the analysis when ICROP is used.

Table 1 shows the similar distribution between P and E treated infants for BW and GA as randomised[3] and between those groups of P and E treated infants who developed ROP. The differences noted between P and E treated infants are not significant. For the entire study population there were no significant differences between inborn vs outborn status, 1 and 5 minute Apgar scores, or any of the recognised risk factors for ROP such as respiratory distress syndrome, bronchopulmonary dysplasia, patent ductus arteriosus, or intraventricular haemorrhage. The decrease in incidence of ROP associated with E treatment as well as the increased incidence of sepsis and necrotising enterocolitis in infants with BW of less than 1500 g who received prophylactic pharmacological E treatment for more than 7 days has been previously reported.[1]

Figure 1 presents, on the y axis, the postnatal age (weeks) at first observation of ROP in the right eye of 111 P treated and 96 E treated infants compared with their GA at birth. The best fit regression lines for the two populations are also shown (P treated infants, $r=0\cdot47$ with a slope of $-0\cdot47$, $p<0\cdot001$; E treated infants, $r=0\cdot35$, slope$=-0\cdot48$, $p<0\cdot001$). The figure shows a consistent time lag for postnatal age at onset of ROP in infants treated with vitamin E. The mean age at onset of ROP in the right eye of P treated infants with retinopathy is 6·9 weeks (SE 0·2) compared with a mean age of 8·3 weeks (SE 0·2) for E treated infants with a mean E-P difference of 1·3 weeks (SE 0·3) ($t=4\cdot004$, $p<0\cdot0001$). It is apparent from the figure that, regardless of study medication, infants born earlier in gestation develop ROP at a later postnatal age than infants born later in gestation (note negative slope of regression lines).

Also apparent in Figure 1 but not as easily discernible is the fact that infants born earlier in gestation develop ROP earlier after conception than infants born later in gestation. For example a child born at 27 weeks GA will develop ROP around 34–35 weeks postconceptional age (GA at birth + postnatal age) compared with a child born at 32 weeks who will develop ROP at 36–37 weeks postconceptional age. This is clearly seen in Figures 2 and 3 which plot the postnatal age at onset of ROP vs postconceptional age at onset of ROP for each P treated infant (Fig 2) and for each E treated infant (Fig 3). The mean postconceptional age at onset of ROP in P treated infants is 36·7 weeks (SE 0·22) and in E treated infants is 37·7 weeks (SE 0·30) ($t=2\cdot68$, $p<0\cdot01$). The positive slope of the regression lines for both the P (intercept 33·1, slope +0·52) and E treated (intercept 31·5, slope +0·75) populations again show that infants who develop ROP earlier after conception (y axis) also manifest the retinopathy sooner after birth (x axis).

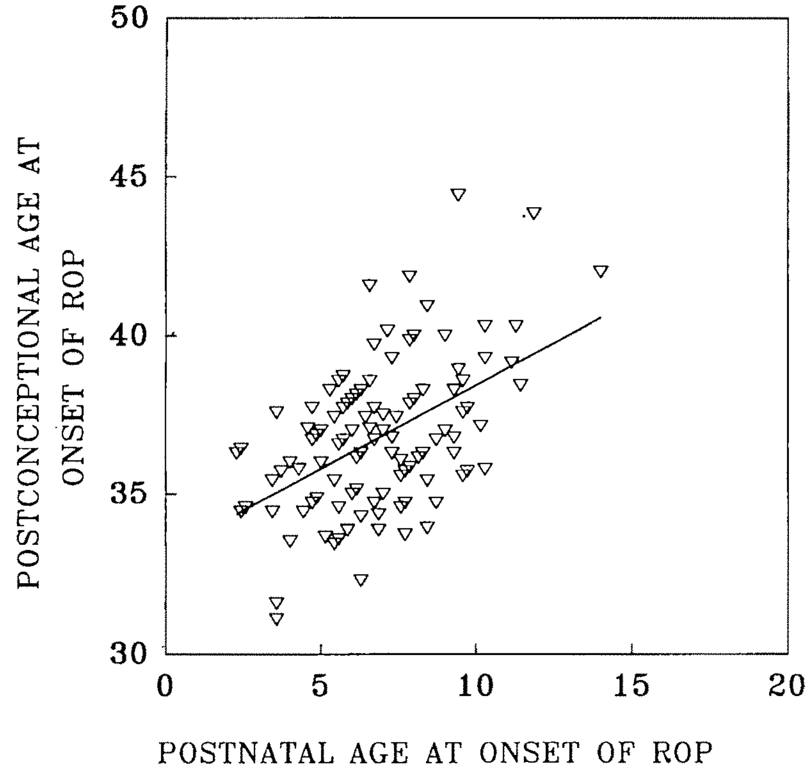
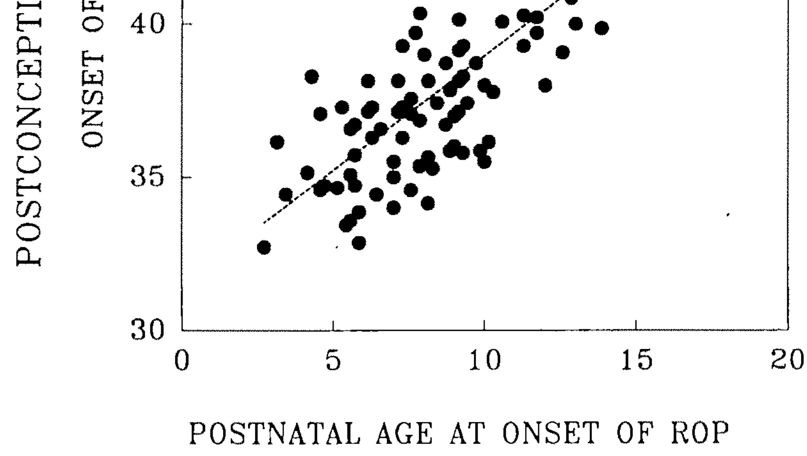


Figure 2 Comparison of postnatal age (weeks) at onset of ROP with postconceptional age at onset of ROP for infants assigned to receive Placebo study medication. The best fit regression line for the P treated infants is represented by the solid line (slope +0·52).

Figure 3 Comparison of postnatal age (weeks) at onset of ROP with postconceptional age at onset of ROP for infants assigned to receive vitamin E study medication. The best fit regression line for the E treated infants is represented by the broken line (slope +0·75).



All of the above findings hold at the same level of significance if onset of ROP is considered to be the appearance of grade 1 ROP by the Schaffer-Quinn classification. The same was also true if appearance of the vascular abnormalities termed preproliferative retinopathy of prematurity (PPRP)[3,4] is used to define the age of onset of visible retinopathy.

Discussion

The issue of when ROP is likely to occur has largely focused on the clinical need to define a practical schedule for performance of screening examinations. Palmer,[9] in a series of 175 infants, concluded that the optimal age for screening for ROP was between 7 and 9 weeks after birth. Flynn,[10] in a larger series of 639 infants, found that most ROP was observed 'between 32 and 44 weeks postconceptional age.' He suggested using the term, 'conceptual age', to 'relate all infants to the same time axis' after conception.[11] In this report, we have concentrated on the complex relationship between 'conceptual age' and postnatal age when ROP is first observed. Our data are unique in their inclusion of infants with a wide range of BW and GA who were examined in the first week after birth, underwent weekly examinations, and who developed ROP. Such a population is no longer available for study because the incidence of ROP in the birth weight groups above 1250 g has fallen dramatically[12] as a result of ongoing improvements in both nutrition and perinatal/neonatal care. Without the inclusion of these more mature infants the accelerating effect on postnatal age at appearance of ROP exerted by perinatal insults early in gestation could not have been seen due to the homogeneity of very low birth weight populations (see Figs 2 and 3).

The earliest ophthalmoscopically visible signs of ROP are vascular abnormalities at the growing ends of the peripheral retinal vessels.[13,14] It is generally accepted that the insults that initiate this retinopathy occur during the perinatal period and are primarily related to degree of prematurity, exposure to an oxygen rich atmosphere, and hypoxic/ischaemic episodes during labour, delivery, and early extrauterine life. These events result in an increased production of oxidant radicals.[15,16] Oxidant radical exposure appears to perturb the complex pattern of cellular events associated with retinal vascular maturation. These perturbations include alterations in membranes of vasoformative mesenchymal elements and nascent capillaries which lead to a delay in the normal time sequence of vascularisation[17,18] and which in some infants result in the early vascular abnormalities of ROP.

Vascularisation of the inner retinal layers, which are farthest from the choroidal circulation, develops in response to the increased oxygen needs of the differentiating retina.[13,14,19] Abnormalities of the developing vessels probably occur during periods of vessel growth and they appear to become manifest later after birth but earlier after conception in infants who are born very early compared with less early in gestation (see Fig 1). This suggests that both the state of retinal development and the time of exposure to the oxygen rich extrauterine environment, with its associated unphysiological perinatal events, influence the time at which the visible changes of ROP occur. If perinatal conditions[1] (an oxygen rich environment, hyperoxia, hypoxia, hypothermia, hypercarbia), independent of ocular growth and development, were sufficient to initiate retinopathy one would expect to see ROP at a constant postnatal age regardless of GA at birth. In other words the regression line for Figure 1 relating GA at birth and postnatal age at onset of ROP would be parallel to the x axis. This is not the case since postnatal age at onset of ROP increases with decreasing GA at birth (Fig 1). If on the other hand the stage of development of the retina solely determined the time when ROP becomes visible one would expect the appearance of ROP at a constant postconceptional age again regardless of GA at birth. For example if all ROP first occurred at 35 weeks after conception the baby born at 25 weeks would develop ROP at the same postconceptional age as the baby born at 30 or 35 weeks of gestation – that is, the postnatal age at onset of ROP would be at age 10 weeks for the 25 week GA infant, 5 weeks for the 30 week GA infant, and at birth for the 35 week GA infant. As is apparent from Figure 1 this is not the case since postconceptional age (GA at birth+postnatal age) at onset of ROP increases with increasing GA at birth.

This observation argues for a complex relationship between immaturity and events which occur during the transition to extrauterine life. We speculate that the most likely explanation for the greater delay in time from birth to appearance of ROP in the more immature infant, compared with the less prematurely born, is the fact that, in terms of thickness and stage of differentiation, the more immature retina takes longer to reach the point at which cellular metabolic demands require ongoing vascularisation. Onset of ROP nevertheless occurs sooner after conception in the baby who is very prematurely born compared with the more mature infant who manifests ROP later after conception but sooner after birth. The perinatal and neonatal insults which lead to initiation and progression of disease are not sustained by the more mature baby as early in the course of vascular development.

The data for P treated infants as presented in Figure 2 emphasise the importance of both perinatal insults and stage of retinal development at introduction to an oxygen rich atmosphere in determining the age at onset of ROP. If there were no or minimal influence of perinatal events then for each week increase in postnatal age at onset of ROP there would be a corresponding increase of 1 week for the postconceptional age at onset of ROP. The slope of the line defining this relationship would be 1·00 and the regression line would intersect the y axis at 45 degrees. This is clearly not the case for data from P treated infants shown in Figure 2 in which the slope of the line is 0·52.

It appears that the relationship between postnatal and postconceptional age at onset of ROP has been altered by prophylactic treatment with E. As seen in Figure 3 the slope of the line showing the data for E treated infants is 0·75, rather than 0·52. This is what one would expect if the contribution of perinatal insults had been decreased, but not eliminated, by antioxidant treatment.

That both stage of development and perinatal events are important in determining age at onset of ROP differs somewhat from the conclusion of Fielder *et al*[20] that the 'age at which ROP is first seen is controlled predominantly by stage of development rather than neonatal events'. It should be pointed out however that these authors also noted that infants with gestational ages less than 28 weeks at birth developed ROP 2 weeks earlier after conception than later born infants (33·7 vs 35·7 weeks, respectively).

New vessel formation in the normally developing retina in both the intrauterine and extrauterine environment is believed to be governed by a graded hypoxic stimulus originating from hypoxia-related angiogenic factors in tissues near the junction of vascularised and non-vascularised retina. If the abnormal vessel formation in the retina with ROP results from oxygen-induced capillary die-back and the associated increase in hypoxia-related angiogenic factors, as suggested by Patz[13] and Ashton,[14] then the area of differentiated retina requiring new growth (or regrowth) of vessels would be the limited area near the junction of vascularised and avascular retina. This band of relative hypoxia would be smallest in the least mature retinas (vascularised only into zone 1) and largest in those retinas with vessels extending well into zone 2 which occupies a much larger area. ROP should occur therefore sooner after conception in those infants born with retinal vascularisation into zone 2. One would not expect the postconceptional age at onset of ROP to be less in the infants born most prematurely with vascularisation confined to zone 1, as was the case in our data (Figs 2 and 3). If however as in the spindle cell theory of ROP,[18 21] the extent of insult to the avascular spindle cell-populated retina (which varies inversely with postconceptional age) determines the magnitude of angiogenic stimulus, then one would expect the magnitude of this stimulus to be greatest in the most prematurely born infants. Such infants would probably manifest more severe retinopathy sooner after conception but later after birth than their later born counterparts. Arguing from these premises our data are better explained by the spindle cell than by the capillary die-back theory of ROP.

Finally what is the significance of the time delay in ROP seen in E treated infants and what is its relevance for the clinician caring for the child at risk for ROP? As seen by the essentially parallel regression lines for P and E treated infants shown in Figure 1 the delay in onset of ROP caused by prophylactic antioxidant administration is remarkably consistent across the study population even for infants below 28 week GA. Kretzer and Hittner[18 21] have suggested that vitamin E would be minimally effective in preventing retinopathy in infants below 28 weeks of gestation because the developing interstitial retinol binding protein transport system cannot efficiently transport vitamin E from the outer to the inner retina prior to that point. However even in these smallest infants they found that vitamin E decreased the overall severity of disease and postponed the age at which sight threatening ROP was seen. The clinical data from this trial, as well as our earlier work,[22] are consistent with this observation and suggest that when postnatal vitamin E does not prevent ROP it nevertheless delays its onset. This amounts to a considerable clinical advantage since the earlier the onset of ROP the more likely it is to progress to severe retinopathy.[23] Furthermore the E related delay in time to peak disease which we observed in this clinical trial[24] would result in an infant who is older and probably more stable when cryotherapy for threshold ROP[25] is indicated. As pointed out in our earlier report[1] the optimal serum level and regimen of prophylactic E supplementation is not certain, but should probably be one that achieves serum total E levels in the physiological range (1–3 mg/dl) soon after birth. Serum E levels in the pharmacological range should *not* be used for prophylaxis but show promise for treatment of severe ROP. The exact mechanism of the delay observed in this study population is open for discussion but it probably hinges on the ability of vitamin E, a biological antioxidant, to stabilise membranes, decrease oxidant damage, and promote healing.[1 2 26 27]

The authors wish to thank Michael E Breton, PhD and Dan Montzka, MD for their help in statistical analysis, Mary Grous for her research assistance, Glen Gole, MD for helpful suggestions with manuscript, and David B Schaffer, MD, who performed a number of the eye examinations reported here.

This work was supported in part by the Retinal and Choroidal Disease Branch of the National Eye Institute, Grant no RO1EY01723. It was presented in part at the Association for Research in Vision and Ophthalmology Annual Meeting, May 1989, Sarasota, FL, USA.

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British Journal of Ophthalmology, 1992, 76, 289–291

Cryotherapy for retinopathy of prematurity – a prospective study

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Accepted for publication
17 October 1991

Abstract

Cryotherapy has been shown to reduce the unfavourable outcome in retinopathy of prematurity with stage 3 threshold disease by 50%. In a prospective study cryotherapy had a favourable outcome in 13 of 24 eyes with stage 3 threshold disease. The visual outcome, refraction, and complications of cryotherapy are discussed.

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness.[1,2] Cryotherapy was first used in the treatment of this condition in the 1970s.[3,4,5,6] However the methods of application and the overall success rate differed.[7,8,9,10] To standardise treatment the multicentre North American Cryotherapy for Retinopathy Study Group trial (CRYOROP) was established in 1986 and the results, published in 1988,[11] showed that the incidence of an unfavourable outcome could be reduced from 43% to 21·5% in treated cases. We present our own experience and results in a prospective study of children treated since 1986.

Materials and methods

All infants born between January 1986 and December 1990 with documented ROP who attended the Children's Hospital, Dublin are included in a prospective study to monitor the long-term effects of premature birth and ROP. Sixteen premature infants (nine male and seven female) who received cryotherapy in this study form the basis for this paper.

Our indications for treatment were based on the criteria defined by the CRYOROP group – that is, stage 3 threshold disease, defined as stage 3+ disease involving five contiguous or eight cumulative 30 degree sectors in zone 1 or zone 2. However we differed from the CRYOROP trial in that we treated both eyes in some infants and stage 4a in one child. Under direct visualisation, using the indirect ophthalmoscope and a cataract probe, cryopexy was applied separately but contiguously for 2–6 seconds until a blanching effect was seen. Treatment was applied to the avascular retina from the ridge to the ora serrata, excluding the ridge. Cryotherapy varied from five consecutive or eight cumulative sectors, as defined by CRYOROP, or involved the whole circumference depending on the severity of ROP. The procedure was carried out in the operating theatre under general anaesthesia. The infants ranged in age from 6–15 weeks at the time of treatment.

Follow-up ranged from 3 months to 5 years. Visual acuity was recorded by fixation pattern, forced choice preferential, Allen's picture cards, or Sheridan Gardiner, depending on the ability of the child. Refraction and other eye abnormalities were also recorded.

Results

Thirteen eyes regressed to normal with peripheral cryotherapy scars only, 11 eyes developed cicatricial disease following treatment, five of these have ectopic maculae and dragging of the disc, six progressed to total retinal detachment. Two of the six eyes had stage 4a disease at the time of treatment, four had vitreoretinal surgery with one retina reattaching after surgery (Table 1).

The visual outcome is summarised in Table 2. Of the 13 eyes with normal posterior poles, 10 in children all born since January 1990 have central steady maintained fixation. Two eyes in children over 1 year of age have 6/6 forced choice preferential (FCP) and one, in a child age 5 years, has 6/12 FCP. Of the five eyes with dragged disc and macula, four in children less than 18 months old have central, unsteady, unmaintained fixation. One aged 3 years has 6/24 FCP. In addition to cicatricial disease three

Table 1 Severity of ROP and retinal outcome

Patient no	Stage of ROP	Clock hours	Zone of ROP	Retinal outcome
1	3	5	2	Cryoscars
2	3	6	2	Cryoscars
	3	8	2	Cryoscars
3	3	8	2	Cryoscars
	3	8	2	Cryoscars
4	3	12	2	Dragged disc and macula
5	3	8	2	Cryoscars
	3	8	2	Cryoscars
6	3	12	2	Total RD
	3	12	2	Dragged disc and macula
7	3	10	2	Cryoscars
	3	8	2	Cryoscars
8	3	12	2	Cryoscars
	3	6	2	Cryoscars
9	3	12	2	Total RD
10	4			Total RD
	4			Total RD
11	3	5	2	Total RD
	3	8	2	Dragged disc and macula
12	3	12	2	Cryoscars
13	3	8	2	Cryoscars
14	3	8	2	Cryoscars
15	3	10	2	Dragged disc and macula
16	3	8	2	Dragged disc and macula

Table 2 Retinal outcome and visual acuity

Visual acuity	Age	Retinal outcome	Number
CSM	<1 year	Normal posterior pole	10
6/6 FCP	>1 year	Normal posterior pole	2
6/12 FCP	5 years	Normal posterior pole	1
CUSUM	<18 months	Dragged disc and macula	4
6/24 Sn	3 years	Dragged disc and macula	1
NPL	<2 years	Total RD	6

of these children have optic nerve hypoplasia. One child has severe hydrocephalus and cerebral atrophy following grade IV intraventricular haemorrhage which makes even basic visual assessment very difficult.

In the 13 eyes with normal disc and macula three have hypermetropia, one has astigmatism, five have myopia of −1·0 DS and two have myopia of −7·0 DS. In four eyes with cicatricial disease all have myopia ranging from −1·5 DS to −8·0 DS. Refraction was not possible in the remaining eyes due to retinal detachment.

One child with initial successful uncomplicated cryotherapy developed a retrolental membrane and total retinal detachment 2 months following cryosurgery. Two eyes developed retinal haemorrhage near the ridge which spontaneously resolved. One other child had severe chemosis which resolved spontaneously after 3 days. Cryopexy was applied under general anaesthesia in 14 infants and apart from assisted ventilation for 24 hours in two infants, no other major anaesthetic problems were encountered.

Discussion

The current theory for the development of ROP is the release of a vasoproliferative factor from the anterior avascular retina which stimulates neovascularisation.[2] Cryotherapy to the ischaemic retina, which is thought to reduce the formation of this vasoproliferative factor,[13] is presently the only effective treatment in established ROP. Therefore effective screening and proper staging are essential. In our unit we screen all infants under 1500 g and under 30 weeks of gestation. We perform the first examination at 6 weeks using the indirect ophthalmoscope and eye speculum. The pupil is widely dilated using 0·5% cyclopentolate and 2·5% phenylephrine.

While we have in the main adopted the CRYOROP criteria treating stage 3 threshold disease, we have treated both eyes in some children and stage 4 in one child. We have used gestational age only in this prospective study. Others[14] have highlighted the concept of postmenstrual or postconceptual age which is calculated as the sum of the gestational age at birth plus the postnatal age at which retinopathy is discovered. They raised the interesting concept that the age at which ROP is first seen is controlled by the stage of retinal development rather than neonatal events.

The CRYOROP group defined a structural unfavourable outcome as (1) a retinal fold involving the macula, and (2) total retinal detachment. In comparing our results 13 eyes have normal posterior poles and 11 have an unfavourable outcome. Five have dragging of the disc and macula, including one eye which had successful retinal repair, and six have total retinal detachment. Our results show that the retinal outcome is better with treatment at early stage 3 threshold rather than late stage 3 or stage 4 (Table 1). Others have also advocated cryotherapy at an earlier stage and have reported good results.[5] Not all eyes with subthreshold disease escape visual disability[16] but the problem we face is that 90% of children with stage 2 regress spontaneously and cryotherapy is a destructive form of treatment with short and long-term complications.

We realise the inaccuracy of our crude visual estimations; however fixation patterns in young infants have been shown to correlate with final visual outcome.[17] It is also important to emphasise that these visions have not been matched with age norms and this will be the subject of a longer follow-up study. Despite these limitations our results highlight a better visual outcome in eyes with normal posterior poles and a poorer outcome in eyes with cicatricial disease, although some maintain at least navigational vision.

The effect of cryotherapy on the final refractive error also needs to be determined by long-term follow-up. It has been suggested that cryotherapy may increase myopia.[18] In this study the eyes with normal posterior poles have refractive errors which range across the board with high myopia in only one child. Those with cicatrical disease, where it was possible to measure refraction, all have myopia. While our numbers are too small to determine statistical significance perhaps it is reasonable to propose that it is the end point of the disease rather than cryotherapy which determines eye growth and the ultimate refractive error.

We applied cryotherapy under general anaesthesia in contrast to the CRYOROP group where general anaesthesia was used in only 27% of cases. We are better able to apply cryopexy in this environment and our anaesthetist and neonatologist is happier with this approach. Apart from chemosis and retinal haemorrhage which spontaneously resolved, the most severe complication was the development of a retrolental membrane and total retinal detachment 2 months following successful cryoapplication in one eye. This eye showed regression of ROP 2 weeks post treatment. This possibly may have been due to the cryotherapy itself rather than progression of ROP. The CRYOROP trial reported ocular complications such as conjunctival haematoma and laceration, retinal, preretinal, and vitreous haemorrhage. Systemic complications in the same group included bradycardia, arrhythmias, and significant apnoea. Brown[19] reported a series with respiratory and cardiorespiratory arrest. In our study cryopexy was applied under general anaesthesia in 14 infants, requiring assisted ventilation in two infants only.

Recently indirect laser therapy to the avascular retina has been advocated as an alternative to cryotherapy.[20] Its advantages include greater control over the degree of ablative therapy required. However it involves an expensive outlay for a new laser system. Cryotherapy is inexpensive, more mobile, widely available, and relatively easy to apply. In our view it will remain the treatment of choice in most centres for the foreseeable future.

In summary cryotherapy works and is presently the most effective weapon in our fight against blindness in ROP. We feel this study is important as it includes not only children with normal posterior poles but also children with cicatricial disease who have maintained navigational vision or better, after cryopexy, who might otherwise have gone blind. The present concept of threshold disease as the cut-off point for treatment of ROP was determined by consensus rather than by scientific data. We feel this criterion may need to be reviewed.

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British Journal of Ophthalmology, 1992, 76, 292–293

Corneal diameter in premature infants

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Abstract

The size of the cornea is important in the diagnosis of primary infantile glaucoma. Reference values regarding eyes of premature infants are scarce. Such data are of special importance in areas such as the Middle East where infantile glaucoma is common and often evident already at birth. The authors have measured the horizontal corneal diameter of the eyes of 127 premature Saudi infants with a gestational age between 23 and 36 weeks and a birth weight ranging from 540 g to 4720 g. The corneal diameter ranged from 7·75 mm to 10 mm. The smallest diameter (7·75 mm) was found in an infant with a gestational age of 23 weeks and having a birth weight of 520 g. The largest diameter (10 mm) belonged to two infants with a gestational age of 34 and 35 weeks and a birth weight of 2250 g and 2240 g respectively. Corneal diameter was positively correlated ($p<0{\cdot}001$) with gestational age and birth weight. Graphs depicting the regression line of corneal diameter on gestational age and of corneal diameter on birth weight together with the 95% confidence limits for individual values are provided for reference.

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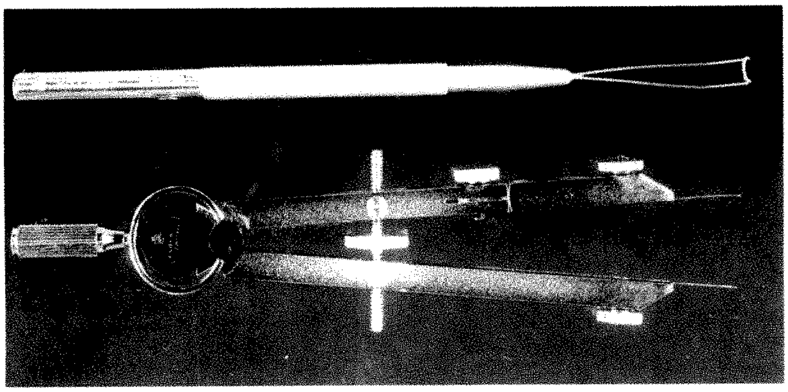
Accepted for publication
3 October 1991

An enlarged, often cloudy, cornea is the most evident sign of primary infantile glaucoma. The presence of these signs already at birth has a bad prognostic significance since it implies an intrauterine onset of the disease resulting in a defective development of the eyeball.[1,2] However a cloudy cornea although of normal size is present in a number of other diseases such as sclerocornea, Peter's anomaly, and congenital hereditary endothelial dystrophy.[3]

Sometimes premature neonates are born with a cloudy cornea and knowing whether this cornea is pathologically enlarged or not may be relevant for the diagnosis. However our knowledge of the corneal diameter of healthy premature eyes is limited to a few cadaver eyes[4] and 37 premature infants.[5]

This paper deals with the measurement of the corneal diameter in 127 premature Saudi infants with healthy eyes.

Figure 1 Modified caliper and retractor used for corneal measurement. In order to minimise the risk of injuring the eye the steel points of the caliper have been replaced with thin, flexible copper wires.



Material and methods

The corneal diameter was measured in 127 premature infants with gestational ages ranging from 23 to 36 weeks the mean age being 33·1 (SD 2·98) weeks. The weight at birth ranged from 540 to 4720 g, the mean weight being 1950 (SD 614) g. The corneal diameter was measured in both eyes but one randomly selected diameter – right or left – from each neonate was used for statistical calculations. Neonates showing ocular pathology, somatic anomalies, or having uncertain gestational age were excluded. The measurement (horizontal diameter, white to white) took place during the first week of life but in six cases was made immediately after death. It was performed with the help of a caliper modified to prevent corneal injury (Fig 1). In order to obtain a good visualisation of the eye the upper lid was cautiously lifted using a wire loop retractor (Fig 1). Often the lid retractor was not applied, gentle manipulation being sufficient to obtain a satisfactory separation of the lids. The caliper reading was translated into mm using a set of finely graduated precision rulers. The meaurements were approximated to 0·25 mm. Virtually all measurements were made by one investigator (KU).

Results

The corneal diameter ranged from 7·75 mm to 10 mm. In the eyes of 16 infants measurements varied by 0·25 mm, in two by 0·5 mm, and were identical in the rest. The smallest diameter (7·75 mm) was found in an infant with a gestational age of 23 weeks and having a birth weight of 520 g. The largest diameter (10 mm) belonged to two infants with a gestational age of 34 and 35 weeks and a birth weight of 2250 g and 2240 g respectively.

The corneal diameter correlated positively with the gestational age (Fig 2) and with birth weight (Fig 3). In both cases the correlation coefficient was significant at 99% level being 0·827 for the diameter and the age, and 0·746 for the diameter and the weight. The 95% confidence interval for the mean and the 95% confidence interval for individual values are also shown in Figures 2 and 3.

Discussion

The mean horizontal diameter of human cornea at birth is reported to be 10·0 mm.[6] With regard to the corneal diameter of premature infants no data are available in the literature. According to this study in 127 premature babies with gestational ages between 23 and 36 weeks the corneal

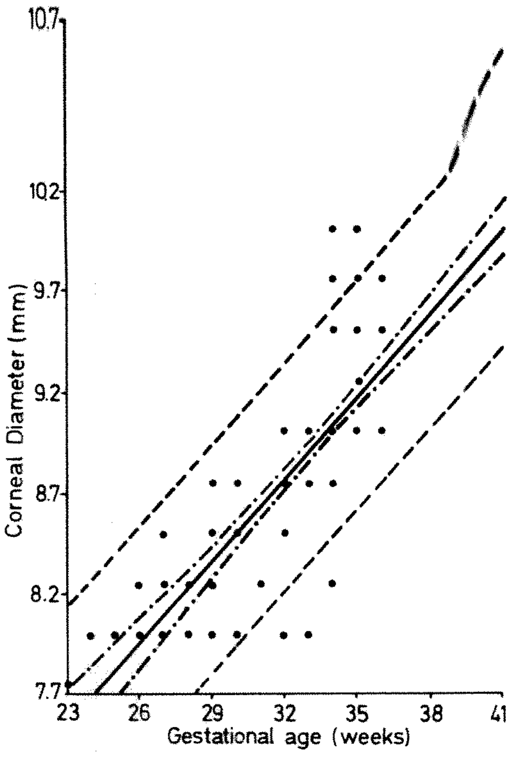


Figure 2 Regression of corneal diameter (mm) on gestational age (weeks). The solid line is the best fit regression line. Inner dotted lines represent the 95% confidence limits for the predicted mean corneal diameter. Outer dotted lines represent the 95% limits for individual diameter values.

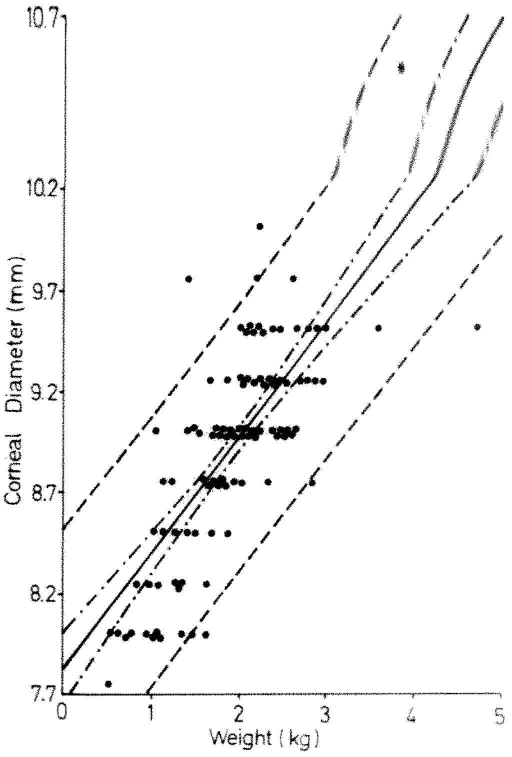


Figure 3 Regression of corneal diameter (mm) on birth weight (kg). The solid line is the best fit regression line. Inner dotted lines represent the 95% confidence limits for the predicted mean corneal diameter. Outer dotted lines represent the 95% limits for individual diameter values.

diameter ranged from a minimum of 7·75 mm to a maximum of 10 mm. There was a clear positive correlation between corneal diameter and gestational age or birth weight.

The walls of neonatal eyes, and even more so those of fetal eyes, are distended by an increased intraocular pressure because the corneal and scleral collagen has not yet sufficiently hardened.[7] Before the age of 6 months the rigidity of the cornea is less than that of the sclera; consequently the cornea enlarges more rapidly under the influence of an increased IOP.[8] Secretion of aqueous humour presumably begins before birth as suggested by the findings of some degree of aqueous drainage effective by 17–18 weeks of fetal life.[9] Fetal facility of outflow correlates directly with the diameter of the cornea.[9] The existence of a fetal aqueous humour circulation has recently been corroborated by a scanning electron microscopy study showing by 18–22 weeks of development the presence of a well formed gap system connecting the anterior chamber with the developing intertrabecular spaces.[10] These data underline the importance of the corneal size in the diagnosis of developmental glaucoma in premature neonates and make it necessary to have reference values available. Knowing the normal corneal diameter in these children at different gestational age and birth weight is of special interest in areas such as the Middle East where the disease is common and often evident already at birth.[11]

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British Journal of Ophthalmology, 1992, 76, 294–296

Pigmented epithelial tumours of the conjunctiva

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Accepted for publication
17 October 1991

Abstract

Two out of 60 conjunctival epithelial tumours reviewed between 1973 and 1989 were found to be pigmented. One tumour was a pigmented papilloma and the other a pigmented squamous cell carcinoma. The melanin pigment was found in epithelial tumour cells as well as in macrophages, dendritic melanocytes, and Langerhans cells. The distinction between the latter two types of cells was possible in one of the tumours only. Both tumours were found in dark-skinned white patients without any evidence of conjunctival acquired melanosis.

Both benign and malignant tumours of the cutaneous surface of the eyelid (for example, basal cell carcinoma, seborrhoeic keratosis, etc), at times become pigmented as a result of melanin ingestion.[1-5] However pigmented epithelial tumours of the conjunctiva, especially in white patients, are rarely encountered.[6-15] This finding is attributed mainly to the paucity of melanocytes in the epibulbar conjunctiva.

We present two cases of pigmented conjunctival tumours found in dark-skinned white patients. These tumours represent 3·33% of all conjunctival tumours examined histologically in the past 16 years in the Pathology Department of the Beilinson Medical Center.

Materials and methods

All the conjunctival tumour biopsies performed in the Eye Department at the Beilinson Medical Center between the years 1973 and 1989 were reviewed by two pathologists and their haematoxylin-eosin stained slides were re-examined. These epithelial tumours included those excised from the bulbar, limbal, caruncular, forniceal, and palpebral conjunctiva and were either benign or malignant. When melanin pigment was found in the tumour bleached sections were examined in order to confirm the true nature of the pigment. Additionally immunohistochemically stained slides for S–100 protein were reviewed. Electron microscopic specimens were examined in one case only.

Results

The breakdown of the total series of 60 conjunctival epithelial tumours is presented in Table 1. Among these epithelial tumours only two (3·33%) were found to be pigmented. One tumour was a pigmented squamous papilloma and the other a pigmented squamous cell carcinoma (SCC). The two cases are presented.

Table 1 Conjunctival epithelial tumours (1973–89)

1	Papilloma	42 (70%)
2	In situ SCC	3 (5%)
3	Epithelial dysplasia	8 (13·33%)
4	SCC	5 (8·33%)
5	Pigmented	2 (3·33)

CASE 1

A 65-year-old dark-skinned white male presented with a pigmented conjunctival tumour in his right eye increasing in size over a period of 8 months. His visual acuity was 6/6 in both eyes and the intraocular pressure was normal. Slit-lamp examination revealed a dark-brown coloured, cauliflower-like, exophytic conjunctival tumour abutting the right limbus (Fig 1). There was no evidence of melanosis in the whole conjunctival surface. The skin of both eyelids was completely normal. The tumour was excised and light microscopy revealed an exophytic conjunctival tumour consisting of epithelial cells with marked atypia, pleomorphism, large prominent nucleoli, and melanin-filled dendritic cells (Fig 2). Many atypical keratinocytes contained large amounts of cytoplasmic melanin (Fig 3). According to the electron microscopic examination melanin was also found in macrophages as well as in Langerhans cells and dendritic melanocytes. The Langerhans cells were identified by electron microscopy by the finding of 'Birbeck' granules in their cytoplasm; they were also found to be S–100 positive as were the melanocytes.

Additionally many dyskeratotic cells, mitotic figures, and areas of marked acantholysis were noted in light microscopy. In several areas tumour cells were seen beyond the epithelial basement membrane. The diagnosis of completely excised conjunctival pigmented SCC was made. A 4-year follow-up showed no evidence of metastasis.

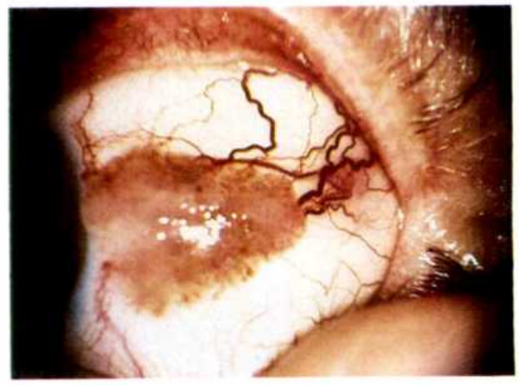

Figure 1 A brown coloured cauliflower-like conjunctival tumour abutting the limbus.

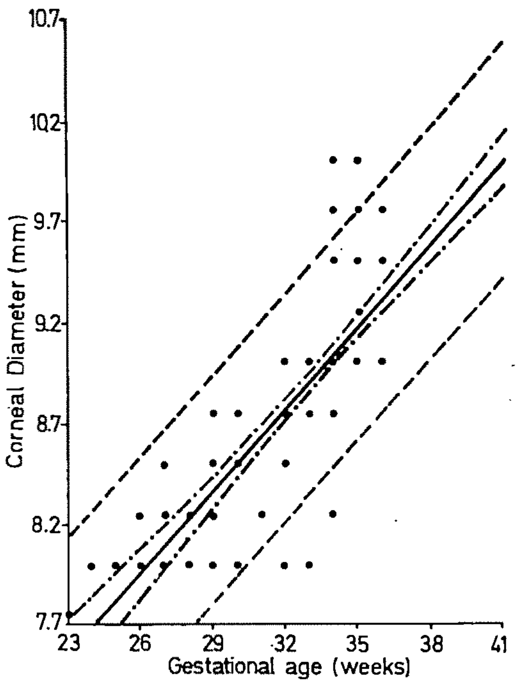

Figure 2 Regression of corneal diameter (mm) on gestational age (weeks). The solid line is the best fit regression line. Inner dotted lines represent the 95% confidence limits for the predicted mean corneal diameter. Outer dotted lines represent the 95% limits for individual diameter values.

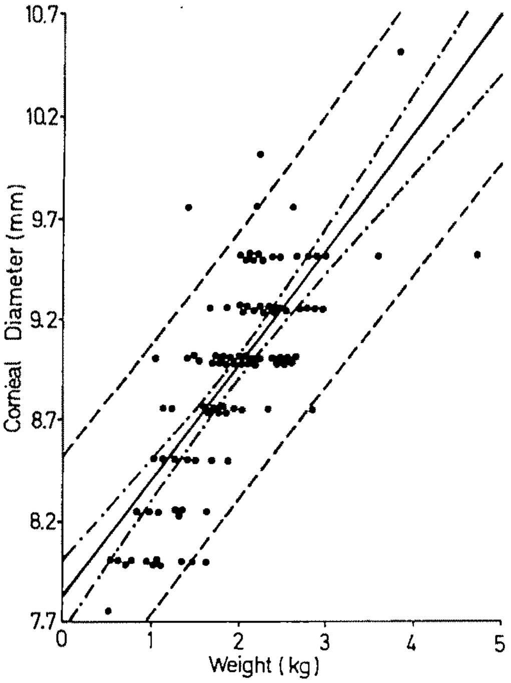

Figure 3 Regression of corneal diameter (mm) on birth weight (kg). The solid line is the best fit regression line. Inner dotted lines represent the 95% confidence limits for the predicted mean corneal diameter. Outer dotted lines represent the 95% limits for individual diameter values.

diameter ranged from a minimum of 7·75 mm to a maximum of 10 mm. There was a clear positive correlation between corneal diameter and gestational age or birth weight.

The walls of neonatal eyes, and even more so those of fetal eyes, are distended by an increased intraocular pressure because the corneal and scleral collagen has not yet sufficiently hardened.[7] Before the age of 6 months the rigidity of the cornea is less than that of the sclera; consequently the cornea enlarges more rapidly under the influence of an increased IOP.[8] Secretion of aqueous humour presumably begins before birth as suggested by the findings of some degree of aqueous drainage effective by 17–18 weeks of fetal life.[9] Fetal facility of outflow correlates directly with the diameter of the cornea.[9] The existence of a fetal aqueous humour circulation has recently been corroborated by a scanning electron microscopy study showing by 18–22 weeks of development the presence of a well formed gap system connecting the anterior chamber with the developing intertrabecular spaces.[10] These data underline the importance of the corneal size in the diagnosis of developmental glaucoma in premature neonates and make it necessary to have reference values available. Knowing the normal corneal diameter in these children at different gestational age and birth weight is of special interest in areas such as the Middle East where the disease is common and often evident already at birth.[11]

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British Journal of Ophthalmology, 1992, **76**, 294–296

Pigmented epithelial tumours of the conjunctiva

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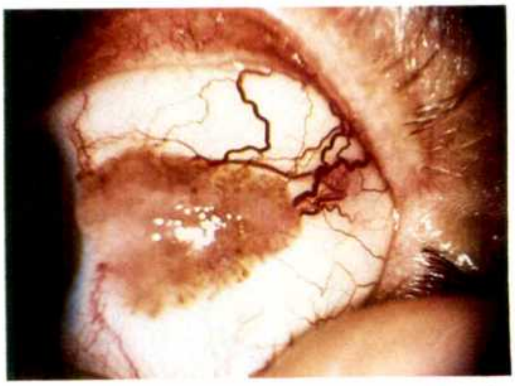

Figure 1 A brown coloured cauliflower-like conjunctival tumour abutting the limbus.

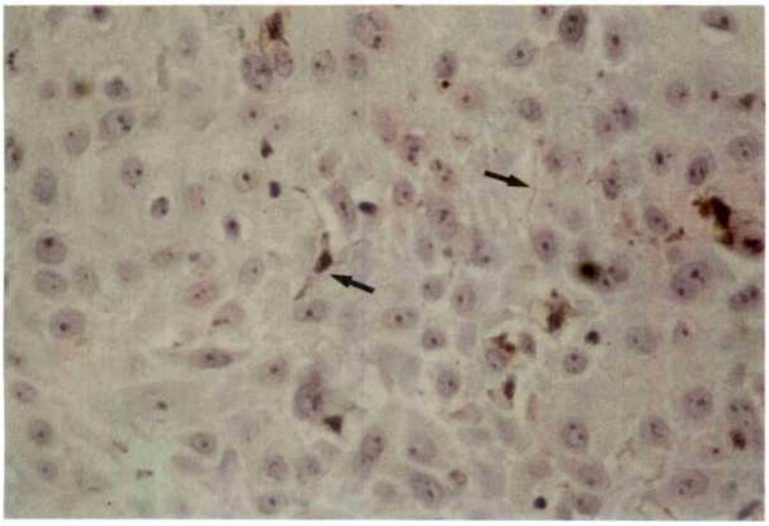

Figure 2 An epithelial tumour consisting of pleomorphic atypical cells with large nuclei and prominent nucleoli; several melanin-filled dendritic cells are noted (arrows) (haematoxylin and eosin, magnification ×270).

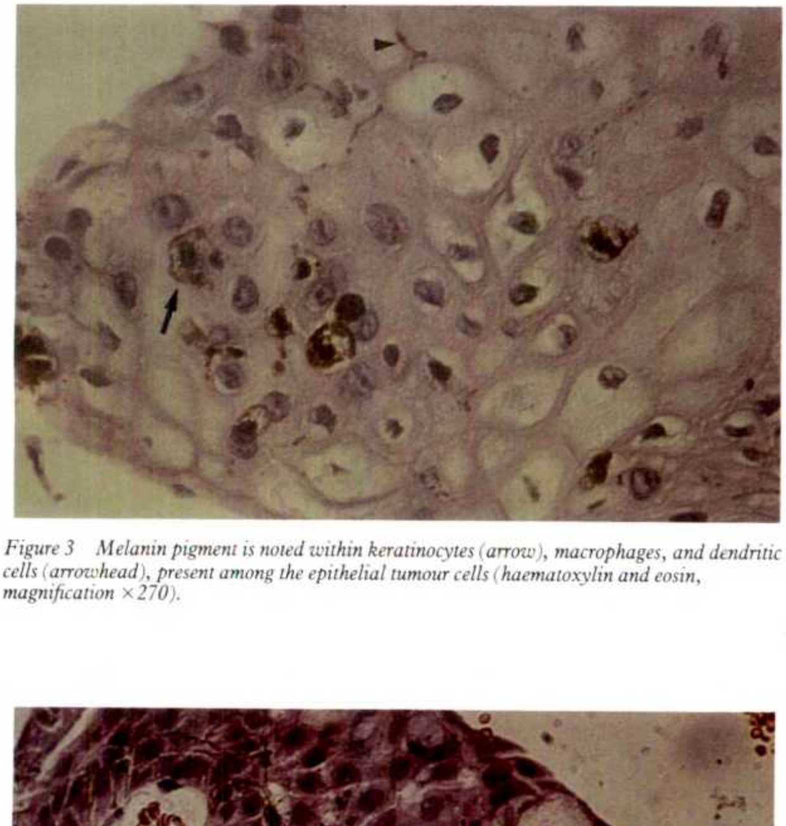

Figure 3 Melanin pigment is noted within keratinocytes (arrow), macrophages, and dendritic cells (arrowhead), present among the epithelial tumour cells (haematoxylin and eosin, magnification ×270).

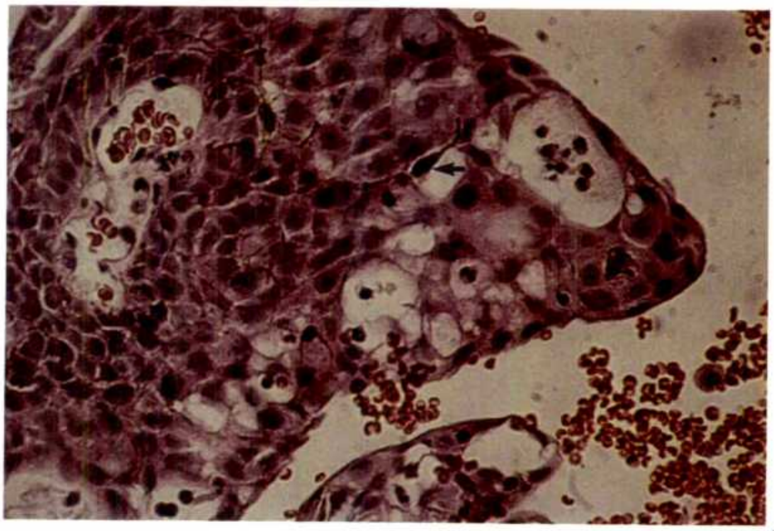

Figure 5 Giant dendritic cells filled with melanin pigment (arrow) are seen among the tumour epithelial cells in which no melanin is found (haematoxylin and eosin, magnification ×270).

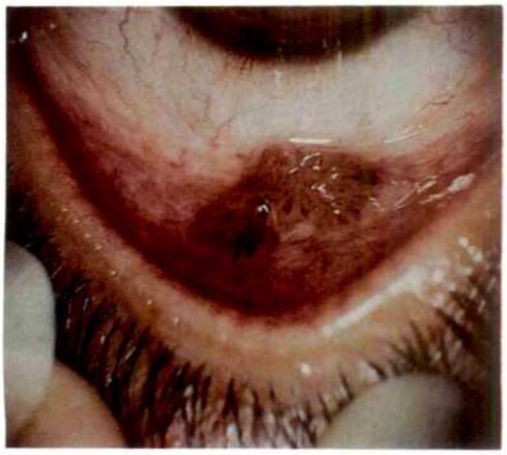

Figure 4 A dark-brown coloured cauliflower-like pedunculated conjunctival tumour protruding from the inferior fornix.

CASE 2

A 22-year-old dark-skinned white male noticed a dark-coloured mass in the inferior fornix of his right eye increasing rapidly in size over the past 4 months.

In addition his visual acuity was 6/6 and the intraocular pressure was normal in both eyes. The slit-lamp examination of the right eye revealed a cauliflower-like, darkly pigmented, pedunculated tumour protruding from the conjunctiva of the inferior fornix (Fig 4). There was no evidence of melanosis in the whole conjunctival surface. The skin of both eyelids was completely normal. The anterior and posterior segments of both eyes were found to be normal.

The tumour's pedicle was excised and light microscopy revealed a conjunctival papilloma consisting of basaloid non-keratinised squamous epithelial cells. Many melanin-filled dendritic cells, some of them being very large, were noted lying in between the tumour cells (Fig 5). These dendritic cells were found to be S–100 positive following immunohistochemical staining (Fig 6). However we could not differentiate between melanocytes and Langerhans cells, either by electron microscopy or by immunohistochemical staining for HLA–DR, as the whole tumoural tissue was primarily fixed in formalin.

It should be noted that there were no tumour cells containing melanin pigment. The diagnosis of completely excised pigmented squamous papilloma of the conjunctiva was made.

Discussion

Pigmented tumours of the conjunctival epithelium are generally a rare finding.[6-15] In blacks they are usually associated with racial conjunctival melanosis.[7 13] SCC arising from the ocular mucous membrane are well known in man and cattle.[5-7] There are considerable geographical variations in the incidence of SCC of the conjunctiva. This tumour appears to be more common in African countries than in other parts of the world.[5 7] Most SCC of the conjunctiva and cornea are non-pigmented.[5-7] Duke-Elder[5] states that surface ulceration of SCC may lead to haemorrhages which colour the tumour almost black. This should be differentiated from pig-

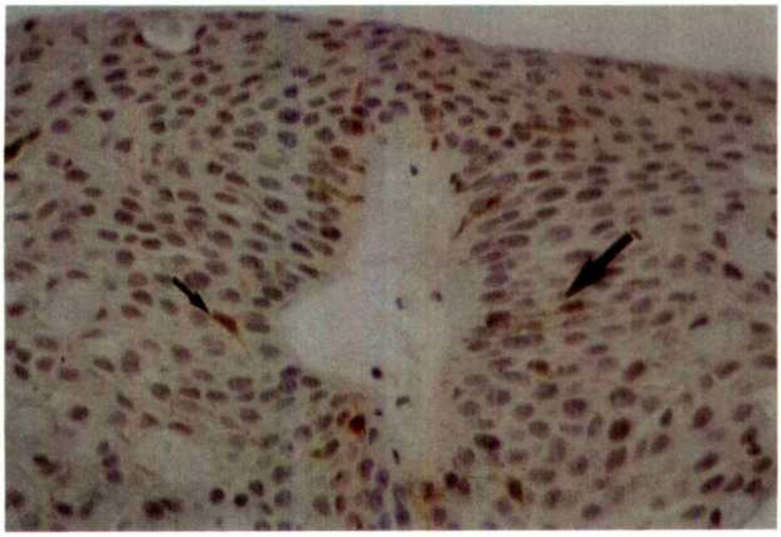

Figure 6 S–100 positive dendritic cells (arrows) are noted between the epithelial tumour cells (immunoperoxidase staining for S–100 protein; magnification ×270).

mentation with melanin in a rare variant of conjunctival SCC which he calls 'melanocarcinoma'.

A pigmented variant of SCC was first described by Noyes,[6] but is apparently very rare especially in white people. Except for its pigmentation this tumour usually resembles the more common non-pigmented exophytic SCC. From the few cases[6 7 9 10] that have been followed for a long period it can be concluded that there is no relationship between the degree of pigmentation and degree of malignancy.[9 10]

Usually in pigmented skin tumours, such as basal cell carcinoma, SCC, and seborrhoeic keratosis, most of the pigment is present within melanocytes.[4 5 10] Similar to our observation other investigators[10] have found that the melanin pigment, present in pigmented conjunctival SCC, is located within macrophages, Langerhans cells, and melanocytes in addtion to tumour epithelial cells. According to the latter authors[4 5 10] the mature melanosomes noted in the neoplastic squamous epithelial cells, without any evidence of premelanosomes, suggest that the neoplastic epithelial cells obtain melanin granules from melanocytes in a manner similar to the normal process of pigmentation of cutaneous squamous epithelial cells.

Papillomas of the conjunctiva are much more common tumours compared with SCC.[8] From the aetiological point of view they may be either of viral nature or neoplastic.[8] Histologically both types are usually non-pigmented. We have found only two reports in the literature on pigmented conjunctival papillomas: one by Grom[11] and the other by Streeten and coauthors.[12] The latter authors[12] report on three cases of inverted conjunctival papillomas one of which was partially pigmented. This lesion was found to contain melanin in many tumour cells and in occasional melanocytes. In contrast we could hardly find any tumour cells containing melanin pigment in our papilloma case; melanin was mainly found in either dendritic melanocytes or Langerhans cells, which unfortunately could not be distinguished from each other. The conclusion drawn from our study is that pigmented tumours of the conjunctiva rarely develop in whites, but they are found in dark-skinned patients but are not associated with conjunctival melanosis. These tumours may cause clinical diagnostic problems as they can be confused with the more common pigmented conjunctival lesions such as malignant melanoma, naevocellular naevus, or primary acquired melanosis undergoing malignant change.

We wonder about the association between the melanocytes, melanin-filled Langerhans cells, and these pigmented epithelial tumours as clinical evidence of melanosis surrounding the tumours was not found. We have no other explanation for this association other than the pre-existence of these two types of cells among the epithelial cells which are the progenitors of the tumour cells. The embryonal origin of these cells is totally different; Langerhans cells are thought to be of bone marrow origin[16] and melanocytes of neural crest origin,[17] while conjunctival epithelial cells are of ectodermal origin. The relationship between these two types of dendritic cells and the epithelial tumour cells is yet to be studied.

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Applications including the names of three referees must be submitted **by May 31, 1992 to:**

Jack Rootman, M.D., F.R.C.S.C.
Professor of Ophthalmology and Pathology
Head, Department of Ophthalmology
2550 Willow Street
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British Journal of Ophthalmology, 1992, 76, 297–299

Spontaneous subconjunctival haemorrhage – a sign of hypertension?

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Accepted for publication
17 October 1991

Abstract

The relationship between the condition of spontaneous subconjunctival haemorrhage (SCH) and hypertension was investigated. Seventy eight patients with SCH and 78 controls with unrelated ophthalmic conditions were compared. Blood pressure (BP) was significantly higher at presentation in the group with SCH at 149 (SD 27)/89 (SD 15) versus 142 (SD 25)/81 (SD 12). The proportion of hypertensives by WHO criteria (systolic blood pressure >160 and/or diastolic blood pressure >95) was 46% on presentation compared with 23% of the control group. The morphology of the lesion did not influence the association with hypertension although there was a suggestion that the group with raised haemorrhages had a tendency to higher systolic blood pressure. It is recommended that all patients with SCH have their BP checked; this will result in the diagnosis of a significant number of new hypertensives.

Subconjunctival haemorrhage (SCH) is a common condition. Definite associations of SCH include trauma (local trauma to the eye or skull base fractures) and conjunctivitis (as part of the inflammatory response). SCH is also recognised in whooping cough, crush injuries, or strangulation where the mechanism is thought to be raised venous pressure.[1] SCH presents more commonly as a spontaneous event without these aetiological factors especially in the elderly or arteriosclerotic.[2-5] It is sometimes stated that this is associated with hypertension[1 6-8] but there have been no detailed studies reported in the literature on the degree of association. In the present study we have measured blood pressure (BP) under standard conditions in patients presenting with spontaneous SCH and a control group and demonstrated that BP is significantly higher in the group with SCH.

Materials and methods

Seventy eight patients presenting with spontaneous SCH at the Glasgow Eye Infirmary, the Tennent Institute of Ophthalmology, and the Royal Alexandra Hospital, Paisley were recruited over a 9 month period. Each patient was assessed initially by an ophthalmologist and subsequently referred for assessment at the MRC Blood Pressure Unit (BPU). The data on each patient were collected independently and compared on completion of the study. A separate group of age-sex matched patients with blepharoconjunctivitis and minor trauma was recruited and in this group the examining ophthalmologist made an assessment of cardiovascular risk factors (as most of these patients were reluctant to attend for review).

Table 1 Mean blood pressure at each visit

	Subconjunctival haemorrhage		*Control*	
	SBP (SD)	*DBP (SD)*	*SBP (SD)*	*DBP (SD)*
Presentation ($n=78$)	149 (27)	89 (15)	142 (25)*	81 (12)†
Follow-up 1 week ($n=46$)	147 (23)	86 (13)	–	–
Follow-up 5 weeks ($n=16$)	149 (27)	89 (15)	–	–

* p=0·09
† p<0·01

INITIAL ASSESSMENT

SCH due to trauma or inflammatory disease was excluded. A history was taken to ascertain whether the patient attributed the haemorrhage to rubbing the eye or to a straining manoeuvre. The morphology of the haemorrhage was recorded, the intraocular pressure measured by Goldmann applanation tonometry, and the fundus examined for hypertensive changes. A single recording of sitting BP was made using a mercury sphygmomanometer.

SUBSEQUENT ASSESSMENT

Each patient was asked to attend the BPU 1 week following his or her initial presentation and 4 weeks after this. Of the SCH group 41 patients attended for the first review when a detailed medical history was obtained, but only 16 attended for second reviews. The blood pressure was measured using a semi-automatic digital sphygmomanometer (Copal, Takeda, Japan) after lying for 10 minutes and a mean of two readings was taken. It rapidly emerged that the control patients were not attending for review so that the protocol was changed to allow the ophthalmologist to assess cardiovascular risk factors in the controls at initial assessment.

Results

There were 78 patients in each group. For the SCH group the mean age was 53 years with a standard deviation of 17 years and a range of 13 to 87. For the control group the mean age was 51 with a standard deviation of 17 years and a range of 13 to 89; 59% of each group were male.

BLOOD PRESSURE

Table 1 shows mean values of systolic and diastolic blood pressure at each visit. Diastolic BP was significantly higher in the SCH group and there was a similar trend in the systolic BP although this failed to reach statistical significance (p=0·09). For the 41 patients with SCH who attended for a second visit there was a correlation between the initial casual reading and the subsequent standardised one (r=0·53 (p<0·001) for systolic and 0·59 (p<0·001) for diastolic). In this subgroup mean BP fell from 154 (SD 26)/92 (SD 15) to 147 (SD 23)/86 (SD 13). Using the WHO criteria for the diagnosis of hypertension (SBP >160 and/or DBP >95)[9] the proportion of hypertensives was 46% at visit 1, 36% at visit 2, and 37% at visit 3. In the control group by comparison only 23% were hypertensive by these criteria.

Five of the patients with SCH and two of the controls fulfilling these criteria for hypertension were known hypertensives. A further seven patients with SCH and eight controls, recorded as high, were diagnosed hypertensives on treatment.

INTRAOCULAR PRESSURE

Intraocular pressure did not differ between the SCH group (15·7 (SD 3·1)) and the controls (15·7 (SD 4·1)) and there was no correlation between IOP and systolic or diastolic BP in either group.

CARDIOVASCULAR RISK PROFILE

Table 2 shows a comparison of the cardiovascular risk profile between the two groups. For reasons mentioned above there are 41 patients in the SCH and 78 patients in the control group for this comparison. There was no significant difference in cardiovascular risk profile with the exception of family history of vascular disease which was significantly higher in the SCH group.

FUNDUS CHANGES

For each patient the examining ophthalmologist was asked to grade the fundus changes from 0–4 by a modified Keith and Wagner classification. Mean fundus score was 0·63 (SD 0·09) for SCH versus 0·33 (SD 0·07) for the controls (p<0·01).

EYE RUBBING AND STRAINING MANOEUVRES

Eighteen patients reported minor antecedent events; their mean BP was 145 (SD 30)/87 (SD 15) compared with 150 (SD 26)/90 (SD 14) for the 60 patients with no causative history. This failed to reach statistical significance (p=0·47, systolic; 0·49, diastolic).

Table 2 Prevalence of cardiovascular risk factors in SCH and control groups. All differences insignificant by χ^2 test, with exception of family history of vascular disease (0·02<p<0·05)

	Subconjunctival haemorrhage (%) (n=*41*)	*Control* (%) (n=*78*)
HBP, personal history	15	12
HBP, family history	34	21
Vascular disease, personal history	5	14
Vascular disease, family history	51	29
Smoking	35	38
Diabetes	10	7

MORPHOLOGY OF SUBCONJUNCTIVAL HAEMORRHAGE

The examining ophthalmologist was asked to state whether the haemorrhage was flat or raised and whether it was bright or dark. There was found to be a mean systolic blood pressure of 145 (SD 27) (*n*=54) in the patients with a flat haemorrhage compared with 157 (SD 25) (*n*=24) for the patients with a raised haemorrhage. These results suggest that a raised haemorrhage is more likely to be suggestive of hypertension but the results do not reach statistical significance (p=0·079). The diastolic means were very close (88 for flat versus 92 for raised). There was no correlation between BP and whether the haemorrhage was bright or dark.

Discussion

Subconjunctival haemorrhage may present to the ophthalmologist, the general practitioner or, occasionally, to the hospital physician. Some authors recommend further investigation of these patients[5, 7] while others suggest that reassurance alone is required.[10, 11]

This study confirms that BP is higher in SCH than in a control group and that there is a high incidence of hypertension in patients with SCH referring themselves to the ophthalmologist which persists on subsequent assessment. This holds true even when the patient attributes the haemorrhage to eye rubbing or to a straining manoeuvre and whether or not the fundus shows early hypertensive changes. The appearance of the haemorrhage was a poor guide to the existence of hypertension with the exception that a raised haemorrhage is associated with a higher mean systolic blood pressure.

The BP recording at the time of presentation may be influenced by a number of factors including observer variability in measurement, anxiety, and the age of the patient. Observer variability in the initial reading seems to be a minor factor since there was a close correlation between first and subsequent (automated) blood pressure measurements. The controlled nature of this study should largely eliminate major influences occasioned by age and anxiety (with the caveat that SCH is an alarming condition, which may explain why the mean blood pressure fell by 7/6 mm Hg by the second visit and the proportion of hypertensives by WHO criteria fell from 46% to 36%).

Our results support the historical view that hypertension may cause SCH but contrast with the published work of Canning[12] who found in a retrospective study that only seven of 100 patients with SCH were hypertensive. (The diagnostic criteria for hypertension were not defined however and an additional 32% of haemorrhages were attributed to eye rubbing or Valsalva manoeuvres.)

It is also stated in the literature that SCH can be a feature of diabetes.[5, 7, 13] In our study there was no significant difference in the prevalence of diabetes between SCH (10%) and controls (7%) and no new diabetics were diagnosed.

The significant difference in fundus scores between SCH and controls is difficult to interpret given the subjective nature of this assessment but may indicate a trend towards arteriopathy in patients with SCH, as may the increased frequency of a family history of vascular disease.

Our patients however had a relatively young mean age (55 (SD 15) years) which, combined with the relative infrequency of manifest cardiovascular disease, suggests that this is a group in which treatment might well be successful in preventing future cardiovascular events. The high incidence of hypertension by established criteria suggests that hypertension may be an important aetiological factor in SCH and we would recommend that all patients with this condition have their BP checked and be referred to the general practitioner. This will result in the diagnosis of a significant number of new hypertensives by the ophthalmologist.

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British Journal of Ophthalmology, 1992, **76**, 300–302

Optimal postoperative refraction for good unaided near and distance vision with monofocal intraocular lenses

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Accepted for publication 24 October 1991

Abstract

Forty five eyes with up to 2 dioptres of myopic astigmatism and up to 1 dioptre sphere either plus or minus following cataract extraction and implantation of a monofocal intraocular lens were examined to assess their unaided visual acuities. Forty three percent were able to see 6/12 and N8, and 60% were able to see 6/12 and N10. Subjects with between 1 and 2 dioptres of myopic astigmatism and virtually no sphere were able to see 6/12 and N10 in 82% of cases. This study confirms the benefits to both distance and near vision of myopic astigmatism as an alternative to multifocal intraocular lenses.

The advent of intraocular lenses has revolutionised the quality of vision obtained by patients following cataract extraction. This is however a fixed focus system and most patients require a spectacle reading lens for good near vision. Multifocal intraocular lenses have been developed to overcome this problem. It has been demonstrated, however, by a number of authors that some patients with monofocal intraocular lenses can attain both good distance and reading vision without the need for a spectacle correcting lens.[1-3]

In a previous study[1] we found that patients with up to 2 dioptres of myopic astigmatism obtained a vision of 6/12 and N8 in 50% of cases. The myopic astigmatism in that study was artificially constructed by correcting the spherical element of the refraction, leaving the myopic astigmatic element uncorrected.

This study was undertaken to assess the uncorrected visual acuities of subjects who had a best manifest corrected refraction of up to 2 dioptres of myopic astigmatism with up to 1 dioptre sphere either plus or minus.

Materials and methods

We studied 45 eyes in 45 patients after cataract extraction with implantation of a J loop intraocular lens into the capsular bag. Patients were admitted consecutively to the study as they presented for routine review and were at least 3 months post cataract extraction. Patients with a corrected visual acuity of less than 6/12 and N6 were excluded from the study.

All patients had preoperative biometry performed on a 3M Digiecho A scan biometer using the SRK Mk 2 formula and were calculated to obtain a spherical equivalent refraction of −1·5 dioptres postoperatively.

Postoperative keratometry was performed on a Haag-Streit Javal-Schiotz keratometer.

The following parameters were measured on each patient.

(1) Unaided and best corrected visual acuities at both near and distance. The distance acuity was measured at 6 metres using an illuminated Snellen chart, and the near at 0·3 metres with illumination from a 60 W light over one shoulder giving approximately 50 ft lm.

(2) Keratometry with either a Canon autokeratometer (18 eyes) or a Haag-Streit Javal-Schiotz keratometer (27 eyes).

All refractions were transposed to a minus cylinder form. Statistical analysis was performed using the χ^2 test.

All cylinders quoted are those obtained by best corrected manifest refraction unless stated otherwise.

Results

The 45 patients comprised 27 males and 18 females of mean age 73 years and age distribution as shown in Figure 1.

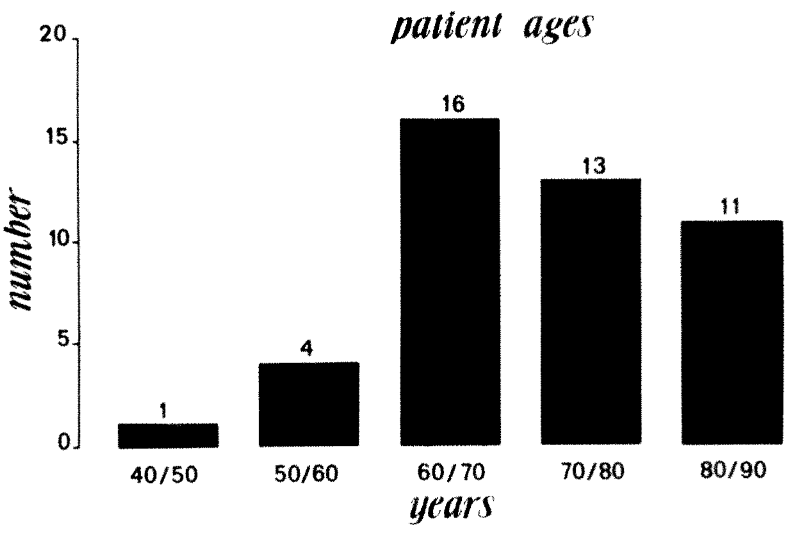

Figure 1 Age distribution of 45 patients following cataract extraction with implantation of an intraocular lens into the capsular bag.

Table 1 Difference in dioptres between corneal astigmatism measured by keratometry and that determined by manifest refraction in 45 eyes after cataract extraction with implantation of a posterior chamber intraocular lens. (All cylinders in plus lens form)

Keratometry minus refraction	*Number*	*%*
+3·25 to +4·0	1	2
+2·25 to +3·0	3	7
+1·25 to +2·0	7	16
zero to +1·0	15	33
zero	5	11
zero to −1·0	11	25
−1·25 to −2·0	3	7

Table 2 Visual acuity levels attained with myopic (−0·5 to −1·0), plus (+0·5 to +1·0), and minimal sphere (−0·25 to + 0·25) with high and low amounts of myopic astigmatism

Sphere	*Cylinder*	*6/12 +N8*	*6/12 +N10*	*Below standard*
+0·5 to +1·0	−1·0 to −2·0	4 30%	6 54%	5 45%
+0·5 to +1·0	Zero to −0·75	1 33%	2 66%	1 33%
0·25 to −0·25	−1·0 to −2·0	5 48%	9 82%	2 18%
0·25 to −0·25	Zero to −0·75	2 50%	2 50%	2 50%
−0·5 to 1·0	−1·0 to −2·0	6 46%	7 54%	6 46%
−0·5 to 1·0	Zero to −0·75	2 66%	2 66%	1 33%
			45	

Table 3 Difference in axis of astigmatism measured by keratometry and that measured by manifest refraction

Axis difference (degrees)	*No*	*%*
0 to 5	10	23
6 to 10	13	29
11 to 15	9	20
16 to 20	7	16
21 to 25	0	0
26 plus	6	12
	45	100

The algebraic difference in dioptres between the corneal astigmatism measured by keratometry and that obtained by best corrected manifest refraction is shown in Table 1. The astigmatism measured by keratometry was greater than that measured by manifest refraction in 58% of eyes. In only five (11%) eyes did the astigmatism measured by keratometry equal that measured by manifest refraction. In 68% of eyes there was a difference of 1·0 dioptre or less, in 23% between 1·0 and 2·0 dioptres, and in 9% more than 2·0 dioptres with an overall difference of 0·88 dioptres.

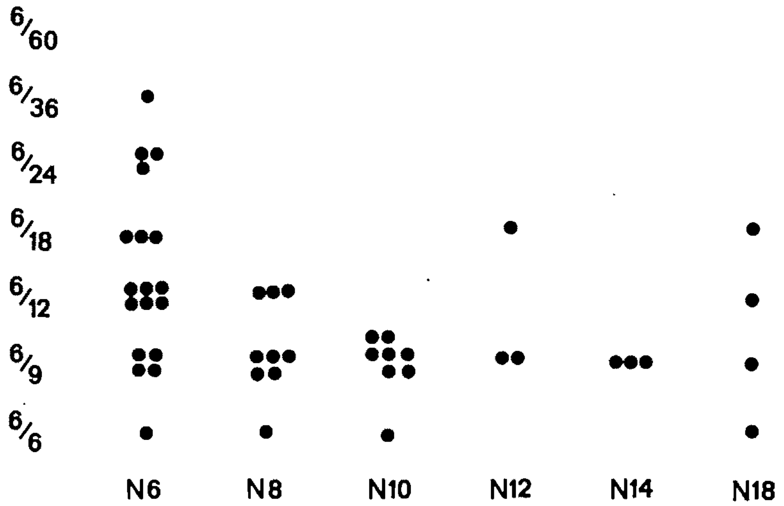

Figure 2 Comparison of unaided distance and near acuities of 45 eyes after cataract extraction with implantation of an intraocular lens into the capsular bag.

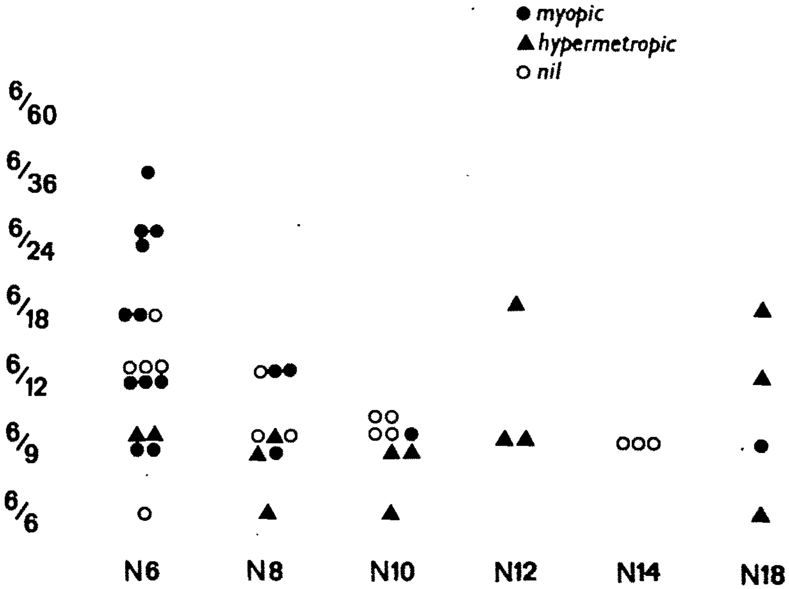

Figure 3 Comparison of distance and near acuities of 45 eyes after cataract extraction with implantation of an intraocular lens into the capsular bag and divided into those eyes with minus (−0·5 to −1·0), plus (+0·5 to +1·0), and minimal (−0·25 to +0·25) sphere.

The uncorrected distance and near acuities of the eyes are shown in Figure 2 with 36 (80%) achieving 6/12 or better, 27 (60%) achieving N8 or better and 35 eyes (78%) N10 or better. However considering both near and distance vision together 20 eyes (45%) achieved 6/12 and N8, and 28 (62%) eyes achieved 6/12 and N10.

Figure 3 shows the uncorrected visual acuities of the 45 eyes separated into plus spheres (+0·25 to +1·0), minus spheres (−0·25 to −1·0), and minimal sphere (+0·25 to −0·25). The spherical power refers to the spherical element of the best refraction lens form. In the myopic group 44% are below standard mainly because of poor distance vision, as expected near vision is very good. Below standard refers to an unaided visual acuity of less than 6/12 and N10. In the hypermetropic patients 43% of the group are below standard mostly because of poor near vision, with a few failing for both near and distance. The group with minimal sphere performed best with only 27% being below standard. If we now divide these three groups into high and low amounts of myopic astigmatism (Table 2) the subgroup with minimal sphere and between 1 and 2 dioptres of myopic astigmatism sees best of all with 82% seeing at least 6/12 and N10.

Statistical analysis of the subgroup with between 1 and 2 dioptres of myopic astigmatism and minimal sphere compared with the other subgroups produces a p value of just more than the 0·05 value. This result is probably due to the low patient numbers in each subgroup.

Discussion

In our study 43% of eyes achieved 6/12 and N8, and 60% achieved 6/12 an N10. These figures are similar to those obtained in a previous study.[1]

The subgroup with between 1 and 2 dioptres of myopic astigmatism and minimal sphere achieved best vision with 82% seeing at least 6/12 and N10. However a statistical analysis shows a p value of just greater than 0·05 (χ^2) when compared with other subgroups within the study. Huber[2] suggested a simple myopic astigmatism of up to 2 dioptres or a compound astigmatism of up to 3 dioptres allowed adequate near and distance vision, as did Datiles.[3]

Most authors believe the phenomenon of pseudophakic pseudoaccommodation to be due to myopic astigmatism, but have pointed out the value of a healthy reactive pupil in obtaining good unaided near and distance vision.[1-3] One author suggested that pupil size was more important than postoperative refraction. However, in a previous study[1] we found pupil size to be insignificant. In that study 85% of eyes had an unaccommodated pupil size 2·5 mm or less and less than 2% had a pupil size greater than 4 mm. All had mobile pupils, we feel that pupil size is unlikely to be significant within this group.

The astigmatism measured by best corrected manifest refraction and that by keratometry showed an average difference of 0·88 dioptres, with the value obtained by keratometry exceeding that obtained by refraction in 58% of cases and refraction by keratometry in 32% of cases. In 11% of cases keratometry equalled refraction.

Some of this discrepancy may be explained by lenticular astigmatism combining with corneal astigmatism producing a change in power and axis as measured by manifest refraction, but this effect is likely to be small. Or in some cases the area of the cornea measured by keratometry may not be in the visual axis. (The difference in axis measured by astigmatism and that by manifest refraction is shown in Table 3.) The most obvious explanation of why the astigmatism measured by keratometry exceeds that measured by refraction in the majority of cases, is that the power of the astigmatism measured at the corneal plane will be greater than that measured at the spectacle plane.

The introduction of multifocal intraocular lenses has generated much discussion on the relative merits of monofocal and multifocal lenses. Some authors have shown great benefits to patients in whom multifocal lenses have been implanted, others have been less enthusiastic.[5] Multifocal lenses are more expensive, there is loss of contrast and reduced image quality, they require very accurate biometry and many designs are sensitive to decentration or pupil size.[5] Monofocal lenses have relatively few problems and if an acceptable unaided distance and near vision is possible with monofocal lenses then that may offer an attractive alternative to implanting multifocal lenses.

A pure myopic astigmatism of 1·5 dioptres axis 180 degrees can be considered a desirable goal for postoperative refraction following cataract extraction and monofocal intraocular lens implantation. This can be achieved by calculating intraocular lens power for −1·5 dioptre sphere and controlling suture tension to give a +1·5 dioptre cylinder at axis 90 degrees.[6] This transposes to give a −1·5 dioptre cylinder axis 180 degrees.

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British Journal of Ophthalmology, 1992, 76, 303–306

Calculation of the power of anterior chamber implants

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Abstract

Ninety seven eyes with anterior chamber implants and a best corrected visual acuity of at least 6/12 were studied, firstly, to compare the predictive accuracies of the commonly used formulas for intraocular lens (IOL) power calculation and, secondly, to determine the effect of optimising the 'A' constant on the predictive accuracies of the empirical Sanders-Retzlaff-Kraff (SRK) formulas. The accuracies of the empirical formulas (SRK and SRK II) were generally similar to those of the theoretical formulas (Binkhorst II and Colenbrander-Hoffer). However the original SRK formula was more accurate than the two theoretical formulas in long eyes and in all eyes overall. Optimisation of the 'A' constants did not improve the predictive accuracy of the empirical SRK formulas.

Several formulas are available for calculating intraocular lens (IOL) power. Theoretical[1-3] formulas were used in the initial stages followed by the development of more accurate empirical[4-7] formulas. The two commonly used theoretical formulas are the Binkhorst II[8] and Colenbrander-Hoffer[9] but the Sanders-Retzlaff-Kraff or SRK regression formula[7] is presently the most commonly used IOL power calculation formula and this has recently been modified (SRK II)[10] to take into account the non-linear relationship between axial length and IOL power. The predictive accuracy of the newly described SRK II formula was better than the original SRK formula in posterior chamber IOLs.[10 11] In anterior chamber IOLs, however, the SRK II formula was found to be less accurate than the original SRK formula and both of them were less accurate than the Binkhorst II formula.[12] A literature search revealed only a limited number of studies on the performance of various IOL power calculation formulas in anterior chamber IOLs.

The use of optimised, rather than manufacturer recommended, constants has been reported to improve the predictive accuracy of the empirical SRK and SRK II formulas in posterior chamber lens implantation.[10 11 13-17] Comparable information is not available for anterior chamber IOLs. This study was carried out, firstly, to compare the predictive accuracies of the commonly used IOL power calculation formulas and, secondly, to determine the effect of optimising the 'A' constant on the predictive accuracies of the two empirical SRK formulas in anterior chamber IOL implantation.

It must be noted that apart from the commonly used IOL power calculation formulas evaluated in this study various other formulas have recently been introduced including the Holladay[18] and SRK/T[19] formulas, both of which combine the theoretical and empirical approaches.

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Accepted for publication 24 October 1991

Material and methods

All cases of anterior chamber IOL implantation performed at our hospital, either as a secondary procedure for aphakia or following rupture of the posterior capsule in intended extracapsular extraction, between January 1984 and January 1990 were reviewed. We excluded cases of combined trabeculectomy and anterior chamber IOL implantation, and also if best corrected postoperative visual acuity was <6/12 or if postoperative refraction data were incomplete. The 97 eyes with anterior chamber IOLs which met the inclusion criteria were studied to evaluate the predictive accuracies of the various IOL power calculation formulas.

All the implantations were performed by two surgeons using indentical surgical techniques. The anterior chamber lenses implanted were of the same style and made by a single manufacturer – Kelman Multiflex MT Series (Cilco).

IOL power was calculated from measurements of axial length and corneal curvature. Axial length was measured by applanation (A scan ultrasonography) using the Cilco Sonometrics Digicon. Corneal curvature was measured with a Topcon OM-4 keratometer. The software program within the ultrasound equipment was used to calculate the emmetropic IOL power and the predicted postoperative refraction for multiple IOL powers based on the SRK or SRK II formulas with the manufacturer recommended 'A' constant of 115·3. The actual power of the IOL implanted by the surgeon in each case depended on the refractive needs of the patient and the state of the lens and the refraction in the fellow eye. Postoperative refraction used in this study were carried out between 8 and 12 weeks postoperatively when spectacles were prescribed.

Each of two theoretical and two empirical formulas, with the respective manufacturer recommended constant ('A' constant or anterior chamber depth), was used to predict the postoperative refraction in each patient for the lens power implanted by the surgeon. The value (in dioptres) of the difference between the predicted postoperative refraction and the actual postoperative refraction (spherical equivalence in dioptres), termed the predictive error, was computed in each individual case, for the four formulas under evaluation.

The predictive accuracies of the four formulas evaluated were compared on the basis of mean 'absolute' predictive error and its standard deviation, the range of predictive errors, and the distribution of the predictive errors (percentage of cases with actual postoperative refraction within 1 or 2 dioptres respectively of predicted postoperative refraction).

In the second part of this study, the SRK and SRK II formulas were solved to derive the respective optimised 'A' constants based on measurements of axial length (in mm), corneal curvature (in dioptres) and the actual postoperative refraction (spherical equivalence in dioptres). In addition we 'personalised' the SRK II formula by first grouping the eyes according to axial length[10] into short eyes (<22 mm), long eyes ($\geq 24{\cdot}5$ mm), and average eyes and then deriving optimal 'A' constants within each group.

During optimisation of the 'A' constants the following groups of eyes were excluded: obvious errors in axial length or corneal curvature measurement, refractive error due to IOL tilt or malposition, induced surgical astigmatism of $>2{\cdot}5$ D cylinder, and any eye with a predictive error of $>2{\cdot}5$ D in spherical equivalence. These eyes were however included when evaluating the predictive accuracies of the two SRK formulas.

The 'A' constants were optimised using the refraction factors (RFs) recommended with each formula – the SRK formula[2] uses a refraction factor of 1·5, while the SRK II[3] uses 1·25 for emmetropic IOL >14 D and 1·0 for emmetropic IOL ≤ 14 D. The inverse of this refraction factor indicates the amount of change in postoperative refraction that will result for each dioptre of IOL power above or below the IOL power required for emmetropia. The formulas evaluated were: (1) SRK formula with the manufacturer recommended 'A' constant, (2) SRK formula with the optimised 'A' constant, (3) SRK II formula with the manufacturer recommended 'A' constant, (4) SRK II formula with the optimised 'A' constant, and (5) the 'personalised' SRK II formula. Each of the above five formulas was used to predict the postoperative refraction and compute the predictive error in each individual case for the lens power implanted by the surgeon.

Table 1 Predictive error (in dioptres) of the four formulas evaluated in eyes grouped according to axial length

	*Mean (SD)**	*Range*	*p value vs SRK formula*
Short eyes			
AL<22 mm (n=18)			
SRK	1·33 (1·30)	−0·94–3·69	–
SRK II	1·47 (0·88)	−1·68–3·20	NS
Binkhorst II	1·37 (1·13)	−1·12–3·60	NS
Colenbrander-Hoffer	1·44 (0·95)	−1·92–3·20	NS
Average eyes			
AL 22–24·49 mm (n=51)			
SRK	1·22 (1·05)	−1·81–3·42	–
SRK II	1·23 (1·06)	−2·16–3·52	NS
Binkhorst II	1·48 (1·13)	−1·20–3·92	NS
Colenbrander-Hoffer	1·38 (1·05)	−1·76–3·84	NS
Long eyes			
AL≥24·5 mm (n=28)			
SRK	0·82 (0·58)	−2·21–1·34	–
SRK II	1·17 (0·88)	−2·80–2·50	NS
Binkhorst II	1·54 (0·94)	−1·50–3·50	<0·001
Colenbrander-Hoffer	1·77 (0·92)	−1·50–4·00	<0·001
All cases (n=97)			
SRK	1·13 (0·99)	−2·21–3·69	–
SRK II	1·25 (0·99)	−2·80–3·52	NS
Binkhorst II	1·47 (1·05)	−1·50–3·92	<0·05
Colenbrander-Hoffer	1·50 (0·99)	−1·92–4·00	<0·01

*Mean (SD) of absolute predictive error
AL=axial length
n=number of cases
NS=not significant

The predictive accuracies of the five formulas evaluated were compared on the basis of: mean absolute predictive error and its standard deviation, 'average' predictive error (taking into account the plus or minus signs of the predictive errors) and its standard deviation, and the distribution of the predictive errors (number of cases with <1 D or <2 D of predictive error).

STATISTICAL ANALYSIS

In both parts of this study the statistical significance of the differences in the predictive accuracies of the formulas evaluated was assessed using (i) standard error of the difference between means on the mean predictive error of the different formulas, and (ii) χ^2 test on the number of cases with <1 D of predictive error.

Results

Table 1 shows the mean absolute predictive errors of each of the four formulas for anterior chamber IOL implantation in eyes of different axial lengths. There were 18 short eyes (<22 mm), 28 long eyes ($\geq 24{\cdot}5$ mm), and 51 eyes of average axial length (22–24·49 mm). The SRK formula had the smallest mean predictive error overall. This was statistically significant when compared with the Binkhorst II ($p<0{\cdot}05$) and Colenbrander-Hoffer ($p<0{\cdot}01$) formulas but not with the SRK II formula ($p>0{\cdot}1$). The SRK formula also had the smallest mean predictive error within the different subsets of eyes studied but this was not statistically significant except when compared with the Binkhorst II and Colenbrander-Hoffer formulas in long eyes ($p<0{\cdot}001$). The theoretical formulas had larger predictive errors than the empirical formulas in eyes of average and long axial lengths but were similar in short eyes.

The distribution of the predictive errors of the four formulas evaluated in eyes of different axial length groups is shown in Table 2. The predictive errors are depicted as cumulative percentages within 1 dioptre and within 2 dioptres and as percentages over 3 dioptres for each of the various IOL power calculation formulas. The SRK formula had the largest percentage of cases within 1 D of predicted postoperative refraction in short eyes (67%), long eyes (71%), and all cases (70%). However none of the differences in Table 2 were statistically significant.

The manufacturer recommended 'A' constant with the SRK formula was 115·3 for the Kelman Multiflex style of anterior chamber IOL implanted in all the cases. After optimisation the 'A' constant was 116·1 for the SRK formula and 116·2 for the SRK II formula respectively.

The optimised 'A' constants for the personalised SRK II formula were 116·8 for short eyes, 116·3 for eyes of average axial length, and 115·6 for long eyes.

Table 3 shows the predictive errors of the various formulas in eyes of different axial lengths. After optimising the respective 'A' constants both the SRK and SRK II formulas showed a reduction in mean absolute predictive error and a

Table 2 Distribution of predictive error of the four formulas in eyes grouped according to the axial length

	SRK	*SRK II*	*Binkhorst II*	*Colenbrander-Hoffer*
Short eyes				
AL <22 mm (n=18)				
* <1 D	67	33	56	50
* <2 D	78	67	78	78
† >3 D	6	6	6	6
Average eyes				
AL 22–24·49 mm (n=51)				
* <1 D	71	73	65	65
* <2 D	90	92	88	86
† >3 D	2	2	4	4
Long eyes				
AL ≥24·5 mm (n=28)				
* <1 D	71	64	46	43
* <2 D	93	82	82	86
† >3 D	–	–	4	4
All cases (n=97)				
* <1 D	70	63	58	56
* <2 D	89	85	85	82
† >3 D	2	2	4	4

AL=axial length
n=number of cases
*cumulative percentages
†percentage of all eyes

Table 3 Predictive errors of the formulas evaluated in eyes grouped according to axial length

	Predictive error (in D)	
	Average Mean (SD)	*Absolute Mean (SD)*
Short eyes		
AL <22 mm (n=18)		
SRK	1·10 (1·53)	1·33 (1·30)
Optimised SRK	0·68 (1·42)	1·23 (1·04)
SRK II	0·51 (1·71)	1·47 (0·88)
Optimised SRK II	−0·37 (1·63)	1·39 (0·77)
Personalised SRK II	0·03 (1·61)	1·19 (0·84)
Average eyes		
AL 22–24·49 mm (n=51)		
SRK	0·70 (1·46)	1·22 (1·05)
Optimised SRK	0·26 (1·51)	1·19 (0·81)
SRK II	0·67 (1·47)	1·23 (1·06)
Optimised SRK II	0·19 (1·50)	1·17 (0·83)
Personalised SRK II	0·08 (1·51)	1·16 (0·80)
Long eyes		
AL ≥24·5 mm (n=28)		
SRK	−0·02 (1·04)	0·82 (0·58)
Optimised SRK	−0·26 (1·29)	1·13 (0·99)
SRK II	0·50 (1·41)	1·17 (0·88)
Optimised SRK II	0·14 (1·26)	0·95 (0·83)
Personalised SRK II	0·28 (1·28)	0·85 (0·81)
All cases (n=97)		
SRK	0·57 (1·40)	1·13 (0·99)
Optimised SRK	0·13 (1·45)	1·11 (0·87)
SRK II	0·59 (1·47)	1·25 (0·99)
Optimised SRK II	0·17 (1·45)	1·21 (0·83)
Personalised SRK II	0·11 (1·44)	1·08 (0·81)

AL=axial length
n=number of cases
SD=standard deviation

tendency for the mean 'average' predictive error to be closer to zero with one exception: in long eyes the mean 'average' predictive error of the SRK formula moved away from zero. The personalised SRK II formula had the lowest mean absolute predictive error and the closest to zero mean 'average' predictive error except in long eyes (Table 3). After optimisation of the 'A' constant the SRK formula ($p<0·04$), SRK II formula ($p<0·05$), and the personalised SRK II formula ($p<0·03$) showed a statistically significant reduction in the mean 'average' predictive error when all the eyes were considered.

Table 4 shows the cumulative percentages of cases with actual postoperative refraction within 1 D and within 2 D of the predicted postoperative refraction and also the percentage of eyes with more than 3 D of predictive error for the five formulas evaluated. None of the differences were statistically significant.

Discussion

In this study of commonly used IOL power calculation formulas in anterior chamber IOL implantation the predictive accuracy of the SRK II formula was similar to that of the SRK formula and two theoretical formulas, Binkhorst II and Colenbrander-Hoffer. The SRK formula was similar to the two theoretical formulas in short and average eyes but was more accurate in all the eyes as a whole and in long eyes.

Table 4 Distribution of predictive errors of the various formulas evaluated in eyes grouped according to axial length

	SRK	*Opt SRK*	*SRK II*	*Opt SRK II*	*Pers SRK II*
Short eyes					
AL <22 mm (n=18)					
* <1 D	67	72	33	39	61
* <2 D	78	94	67	72	94
† >3 D	6	6	6	6	–
Average eyes					
AL 22–24·49 mm (n=51)					
* <1 D	71	71	73	73	75
* <2 D	90	90	92	92	94
† >3 D	2	–	2	–	–
Long eyes					
AL ≥24·5 mm (n=28)					
* <1 D	71	79	64	75	86
* <2 D	93	96	82	96	96
† >3 D	–	4	–	4	–
All cases (n=97)					
* <1 D	70	73	63	67	75
* <2 D	89	93	85	90	95
† >3 D	2	2	2	2	–

AL=axial length
n=number of cases
*cumulative percentages
†percentage of all eyes

In Richards and Steen's report of anterior chamber IOLs,[12] the Binkhorst II theoretical formula was more accurate than the SRK and SRK II empirical formulas. This conclusion is not supported by our findings. This may be because several factors affect the accuracy of the IOL power calculation formulas. These include the method of ocular biometry, the surgical technique, the type and style of IOL, the IOL manufacturer, and the axial length of the operated eye.[11 13 20] In view of this we recommend that each ophthalmic surgeon should select the most accurate formula for his/her own practice by comparing the performance of the various formulas in a sample of his/her own patients after standardising the factors that affect IOL power calculation.

The manufacturer recommended constants were used in this study since the aim was to evaluate the comparative performance of the various IOL power calculation formulas in anterior chamber IOLs. The use of optimised constants reportedly improves the accuracy of various IOL power calculation formulas in posterior chamber intraocular lenses.[10 11 14–17 19] This result has not yet been demonstrated with anterior chamber IOLs.

In the second part of this study of anterior chamber implants we focused our attention on the empirical SRK formulas (SRK and SRK II) mainly because they are highly accurate, widely utilised, and their 'A' constants can be readily optimised unlike the constants used by the theoretical formulas.[8–11 13–17 21–28]

We did not evaluate the recently developed SRK/T formula[19] which is a combination of the empirical and theoretical approaches because (i) at present it is neither readily available nor widely used, (ii) it was not superior to the more commonly used SRK II formula except in eyes of axial length >28·4 mm,[19] and eyes of this axial length were not encountered in this study population.

The optimisation of the 'A' constants resulted in a statistically significant reduction in the mean 'average' predictive error, but there was no significant increase in percentage of cases within 1 D of predictive error. This may be due to the relatively small number of eyes studied. Presently we are undertaking a larger study to determine if the observed statistically significant reduction in the mean 'average' predictive error after optimisation of the 'A' constant translates into a significant increase in predictive accuracy of the empirical SRK formulas in terms of the percentage of cases within 1 D of predictive error.

We thank Sister A E Lewis for administrative help and M Lynch for help with the computerised data analysis.

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British Journal of Ophthalmology, 1992, 76, 307–309

MINI REVIEW

Radiotherapy and ophthalmology: time for a friendly re-acquaintance

Many ophthalmologists expect radiotherapy to be accompanied by late morbidity and therefore reserve it for desperate situations. The radiation tolerance of ocular and orbital structures is now well appreciated,[1 2] and many sequelae of radiotherapy may be prevented by careful radiation dose and modern techniques. Ophthalmologists should be aware that there is a tenfold difference in dose between the cataract threshold and the dose required to harm the retina by conventional external beam radiation.

Superficial *x* ray therapy

Superficial *x* ray therapy is curative for basal cell and squamous carcinomas of the lids and, with careful fractionation, ectropion, nasolacrimal duct stenosis, and other complications are rarely encountered; the globe is protected by lead 'contact lens' shields placed behind the lids. Conjunctival malignancy (and pterygia) responds well to β-therapy from strontium plaques – made 'double sided' to treat malignancy involving the tarsal as well as bulbar conjunctiva; the β-rays do not penetrate to the lens in cataractogenic doses. Haemangiomas of the lids and conjunctiva regress with radiotherapy,[3] as does the conjunctival Kaposi sarcoma associated with AIDS.[4]

Lacrimal gland malignancy may be improved by radiotherapy after surgery, but this does not compensate for radical surgical clearance where this is possible.[5]

Intraocular uses

Low dose radiotherapy may be beneficial in certain benign ocular conditions. Juvenile xanthogranuloma of the iris is extremely radiosensitive,[6] and diffuse choroidal haemangiomas also respond well. The dose is delivered by a lens-sparing technique developed for retinoblastoma (see below).[5 7]

For localised intraocular tumours the now standard use of iodine-125 and ruthenium-106/rhodium-106 ocular plaque brachytherapy has reduced the dose to the operator, and such plaques are replacing the cobalt plaque in both retinoblastoma and melanoma work. The pure β-emissions of ruthenium (with their intense dose to the tumour base, causing infarction) may have further advantages in melanoma therapy. The proton beam data on ocular melanomas look impressive[8]; this too may owe at least some of its effect to damage to tumour vasculature.[9] However, the proton work needs to be compared prospectively with conventional plaque therapy. There are good data suggesting that orbital radiotherapy reduces the local relapse rate[10] after extrascleral extension of a melanoma.

External beam radiotherapy remains the basis of treatment when focal methods fail to control the spread of retinoblastoma[11 12] (Fig 1). In more advanced disease (where enucleation of an only eye is unacceptable to parents), induction chemotherapy followed by radiotherapy is under intense study with good results.

Other globe malignancies that respond well to radiation are choroidal involvement by leukaemia and metastases from solid cancer. In leukaemic children receiving prophylactic cranial irradiation, the back of the eye receives some radiation and this may explain the lower ocular relapse rate.[13 14] Choroidal metastases (especially from breast carcinoma) may be associated with cerebral metastases, and thus a computed tomography scan is performed before recommending radiotherapy to the eye alone. Similarly, ocular lymphoma is also associated with an increased incidence of intracerebral disease.

Orbital disease

Benign disease of the orbit may respond to low dose therapy now that sophistication of techniques allow protection of the anterior chamber, lacrimal gland, and lens. Thus Langerhans cell histiocytosis (histiocytosis X) of the orbit is one example,[15] and orbital haemangioma may also benefit.[3 15]

The management of Graves' ophthalmology generates considerable debate.[16 17] Radiotherapy has been advocated for many years[18] but only recently have modern methods obviated treatment related morbidity.[18 19] Thus, current radiation methods allow effective treatment for steroid resistant disease – particularly with optic nerve compression, exposure keratitis, and painful orbitopathy. Recent analyses showed that surgical decompression or radiotherapy were effective but that surgical decompression gave a slightly greater decrease in proptosis; however ocular movements were better assisted by radiotherapy.[20 21] This last observation, when coupled with the safe track record of the current technique, may increase the indications for radiotherapy. However, other authors have not found such improvements in ocular motility.[22 23]

Orbital pseudotumours are sensitive to low dose radio-

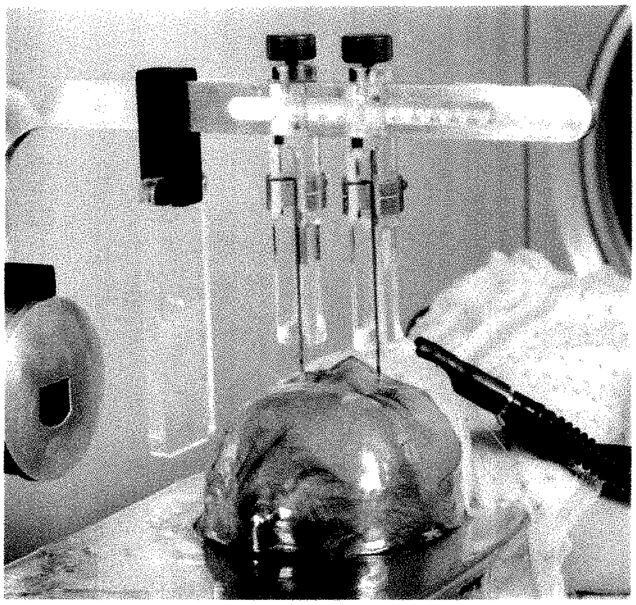

Figure 1 Child on 'set-up' for bilateral lens-sparing retinal radiotherapy (for bilateral retinoblastoma) by this technique.

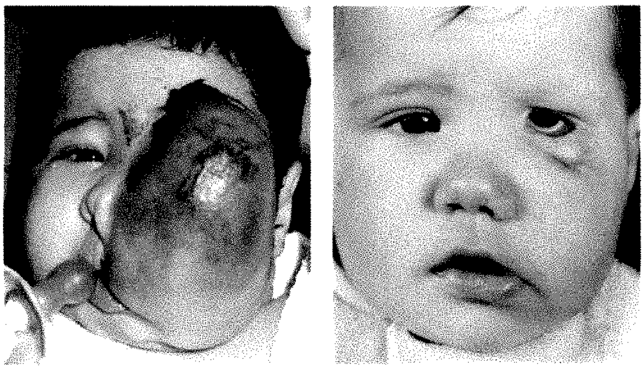

Figure 2 Facial rhabdomyosarcoma of childhood. Left: before treatment. Right: after a modern, aggressive chemoradiotherapy protocol.

therapy and midline ocular structure shielding is practised routinely.[24 25] The patient with benign disease may be warned of the carcinogenic potential, which is of the order of magnitude of 10^{-4}.

True orbital lymphomas contain a highly curable group of extranodal non-Hodgkin's lymphomas. The high grade tumours (approximately 20%), and those with extraorbital extension, require chemotherapy first. The majority of lymphomas are low grade B tumours confined to the orbit; and relatively low dose radiotherapy is curative.[26]

Orbital sarcoma in childhood is usually embryonal rhabdomyosarcoma with a good prognosis (following a chemoradiotherapy programme). These tumours are usually confined to the orbit and such patients have a more than 80% survival rate on current treatment protocols. Late effects due to radiation have recently been reported[27] with a radiation dose prescription of 5000–6000 cGy in 200 cGy fractions. In current protocols the total dose is 4000–4500 cGy in lower daily dose fractions and the late sequelae may be confidently predicted to be lower. Alveolar histology (approximately 10%) or extraocular spread may demand the higher dose (Fig 2). Adult sarcomas of the orbit are more resistant, and surgery and radiotherapy are the mainstays of treatment, with continued debate as to whether adjunctive chemotherapy has a role. Equally debated is the order: preoperative radiotherapy (to facilitate surgical excision with clear margins) versus postoperative radiotherapy (to sterilise microscopic disease left behind).

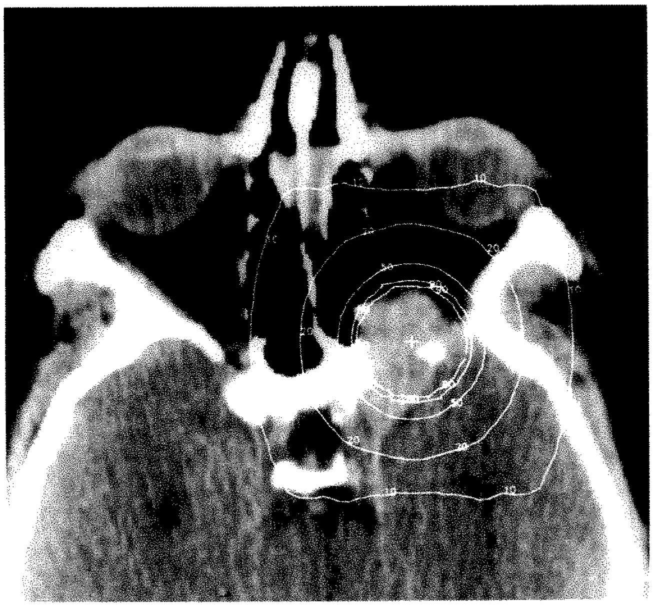

Figure 3 Transaxial computed tomography (CT) scan cut showing recurrence of prolactinoma (following trans-sphenoidal pituitary surgery and radiotherapy) growing through the optic canal into the orbit. Using modern, stereotactically mapped, focal radiotherapy (St Bartholomew's method) the lesion was irradiated to obliterative dose. The patient was already blind in the ipsilateral eye, but the chiasm did not receive a high (re-treatment) dose. Subsequent CT scans show progressive disappearance of the prolactinoma.

Optic nerve gliomas receive radiotherapy if they extend back to the chiasm with deteriorating vision. Optic nerve meningiomas in adults have also been treated by radiotherapy, with anecdotal cases of improved vision after carefully fractionated radiotherapy.[28 29]

Occasionally, difficult tumours occur at the back of the orbit, extending through the optic canal intracranially. A recently introduced focal stereotactic external beam radiotherapy method is now available to deliver extremely high doses to streotactically mapped lesions anywhere in the cranium; the isodoses fall off very sharply at the target perimeter. Of proved use for intracerebral AVMs this technique may be useful in orbital disease. Using the St Bartholomew's focal method, we have recently treated a prolactinoma (resistant to bromocriptine and previous external beam radiotherapy) which had extended from the pituitary fossa through the optic canal to the back of the orbit. A very high treatment dose was delivered and the tumour has regressed but the critical point is that the abutting (and previously irradiated) optic chiasm received less than 20% of the treatment dose (Fig 3). Such technology has also been used for focal treatment of choroidal melanoma in lieu of protons[30] and will have further applications for locally aggressive tumours, particularly at the orbital apex.

In summary, modern radiotherapy has much to offer patients with ocular problems. Knowledge of the radiobiological tolerance of normal ocular structures, enhanced technical precision, and better appreciation of limits of usefulness and morbidity pitfalls have all led to improved therapeutic ratios (success: morbidity).

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British Journal of Ophthalmology, 1992, **76**, 310–312

CASE REPORTS

Bilateral optic nerve sheath meningiomas in a patient with neurofibromatosis type 2

I A Cunliffe, D A Moffat, D G Hardy, A T Moore

Abstract

A 34-year-old woman who presented with hearing loss and tinnitus was found to have reduced vision bilaterally. Computed tomography scan revealed bilateral acoustic neuromas and bilateral optic nerve sheath meningiomas. The presence of bilateral acoustic neuromas fulfils the criteria for the diagnosis of central neurofibromatosis (neurofibromatosis type 2). Although this is the first report of bilateral optic nerve sheath meningioma in neurofibromatosis type 2, meningiomas are commoner in this dominantly inherited disorder, than in its absence and both forms of central nervous system tumour may be caused by loss of tumour suppressor genes on chromosome 22.

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Accepted for publication
31 October 1991

Optic nerve sheath meningiomas are uncommon, and though they may present at any age they are predominantly seen in middle aged females. They are unilateral in most cases.[1-4] The usual presentation is with slowly progressive visual loss, and most patients have evidence of field loss and optic atrophy or disc swelling at presentation.[1-5] Opticociliary shunt vessels are found on the optic disc in about 20% of cases.[3] Other findings include mild axial proptosis, limited ocular movements, and gaze evoked amaurosis.[5] Optic nerve meningiomas are thought to be more common in patients with neurofibromatosis than in general,[1,2,4] when they are usually unilateral. Bilateral optic nerve sheath meningiomas are rare and in none of the reported cases[3-13] has there been any evidence of neurofibromatosis.

We report on a patient with neurofibromatosis (type 2) who had evidence of bilateral acoustic neuromas and bilateral optic nerve sheath meningiomas, causing a dual sensory impairment.

Case report

A 34-year-old woman presented with an 18-month history of tinnitus, increasing deafness in the right ear, and numbness of the right cheek. She had been otherwise well and the only other relevant history was that she had a longstanding right convergent squint and associated amblyopia. She had undergone surgery for right squint at age 7 years.

On examination she had reduced hearing in the right ear, reduced sensation in the distribution of the second division of the right trigeminal nerve, and evidence of mild ataxia. The visual acuity was counting fingers in the right eye and 6/6 in the left eye. Colour vision testing with Ishihara plates was normal in the left eye, but she was unable to recognise any plates with the right. There was a 3 mm right proptosis, and a cover test revealed a small right divergent squint. Ocular movements of the right eye were full, but she had limitation of elevation,

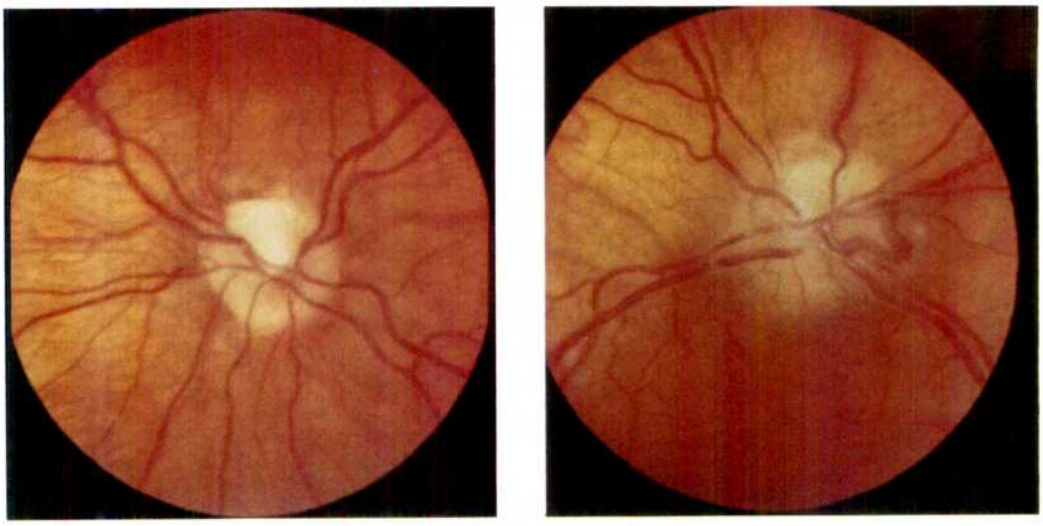

Fig 1A

Fig 1B

Figure 1 Photographs of optic discs showing bilateral pallor and mild swelling of the nerve fibre layer. A: Right disc. B: Left disc.

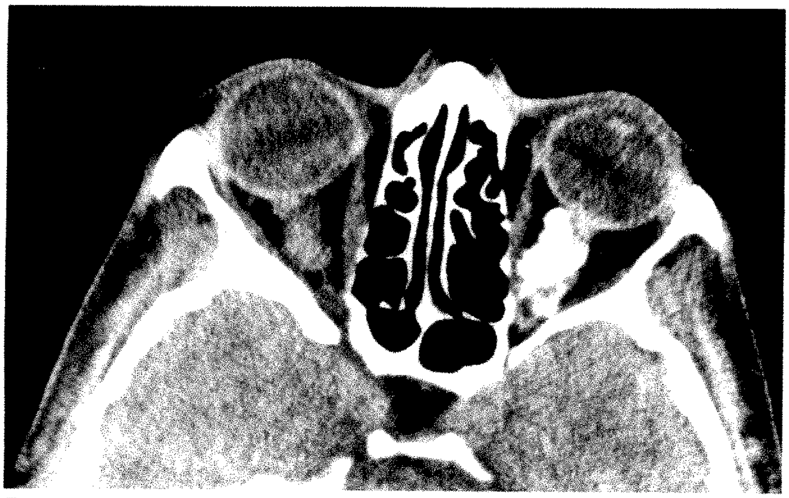

Figure 2 CT scan showing thickened calcified left optic nerve tumour and thickened irregular right optic nerve.

abduction, and adduction of the left eye. There was bilateral gaze-evoked nystagmus. Corneal sensation was reduced on the right but normal on the left. The lenses were clear, and intraocular pressures were normal. Both pupils reacted to light, and there was no relative afferent pupillary defect.

Slit-lamp examination of the iris was normal, with no evidence of Lisch nodules. Both optic discs were pale and slightly swollen but without any opticociliary shunt vessels (Figs 1A, B). In each eye there was a small slightly raised pale subretinal lesion, with associated fibrosis, lying temporal to the macula, probably representing a choroidal hamartoma. Goldmann perimetry revealed a dense right central scotoma and generalised constriction of the left visual field. Visual evoked potentials were unrecordable to both flash and pattern stimuli in the right eye. In the left eye the only abnormality was a mildly prolonged latency of the pattern VEP.

Computed tomography (CT) scan showed a large right acoustic neuroma and a small left acoustic neuroma. In addition there were bilateral optic nerve lesions. The left optic nerve showed a large calcified mass, and there was an enlarged irregular thickening of the right optic nerve, consistent with bilateral optic nerve sheath meningiomas (Fig 2). Systemic examination revealed no other evidence of neurofibromatosis, and there was no family history of hearing loss or central nervous system (CNS) tumours.

The right cerebellopontine angle tumour was excised via a translabyrinthine approach and histological examination confirmed it to be a benign schwannoma. A postoperative magnetic resonance imaging scan showed the right tumour to have been completely excised and confirmed the presence of bilateral optic nerve tumours with no evidence of chiasmal involvement.

Discussion

The neurofibromatoses are divided into two distinct disorders: neurofibromatosis 1 (Recklinghausen's disease, NF1) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis, NF2). Both are inherited as autosomal dominant traits with a high degree of penetrance. The genes responsible for each type have been mapped, to chromosome 17 for NF1 and chromosome 22 for NF2.[14] The diagnostic criteria for each disorder are given in the Neurofibromatosis Conference Statement.[15] The criteria for NF2 are met if the patient has (1) bilateral eighth nerve masses, or (2) a first degree relative with neurofibromatosis 2 and either a unilateral eighth nerve mass, or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lens opacity. The patient reported here fulfils the criteria for the diagnosis of NF2.

Patients with NF2 typically present with either unilateral or bilateral hearing loss, and most have evidence of disturbed vestibular function.[16-18] Large tumours may involve lower cranial nerves or result in raised intracranial pressure.[16] The ophthalmic manifestations include juvenile posterior subcapsular lens opacities,[19] corneal abnormalities associated with loss of corneal sensation or seventh nerve palsies, papilloedema from raised intracranial pressure, nystagmus, sixth nerve palsy, and less commonly visual pathway tumours as in this case. In contrast to NF1 Lisch nodules are rarely present.[20] In NF2 there is an increased incidence of other central nervous system tumours, which may be of schwann cell, glial, or meningeal origin.[16 18 21 22]

Although the mechanism of tumour formation is uncertain, similarities with the development of non-ocular tumours in the hereditary form of retinoblastoma suggest that there may be loss of tumour suppressor genes in NF2. Acoustic neuromas (like retinoblastoma), occur in a hereditary and non-hereditary form.[14] Patients with the non-hereditary form have unilateral tumours which present later, and do not develop other CNS tumours. In patients with NF2 there is often a family history, the tumours are bilateral and present earlier and there is an increased risk of developing other CNS tumours, particularly meningioma. Both meningiomas and acoustic neuromas[23 24] show loss of chromosome 22 material in the tumour tissue, suggesting that in patients with NF2 (who have a germinal mutation of chromosome 22) tumour formation may result from the loss of the normal allele as a result of a somatic cell mutation.[24] It is unclear, however, whether the mutations responsible for acoustic neuromas and meningiomas are at the same or different loci on chromosome 22.[25] Although unilateral optic nerve meningiomas have been reported in neurofibromatosis,[3 4 26] most reports predate the recognition of the two forms of the disorder, and it is not clear whether these optic nerve tumours are seen predominantly in peripheral or central NF. In the family with NF2 reported by Delleman *et al*[27] one affected member had a unilateral optic nerve sheath meningioma but without acoustic neuroma. The patient reported here is further evidence that optic nerve sheath meningiomas may develop in NF2 and may result from the loss of normal genes responsible for regulating growth of neural tissues.

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British Journal of Ophthalmology, 1992, **76**, 313–315

Malignant melanoma of the optic nerve head in a case of oculodermal melanocytosis

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Accepted for publication
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Abstract

Malignant melanoma of the uveal tract, orbit, and brain have been reported to occur in patients with oculodermal melanocytosis. A 60-year-old Caucasian man with oculodermal melanocytosis developed a malignant melanoma of the optic nerve head in the left eye. This case is the first reported example of a malignant melanoma developing in the optic nerve associated with oculodermal melanocytosis. After presentation the patient refused surgery for 19 months and the progression of the tumour necessitated an exenteration of the orbit.

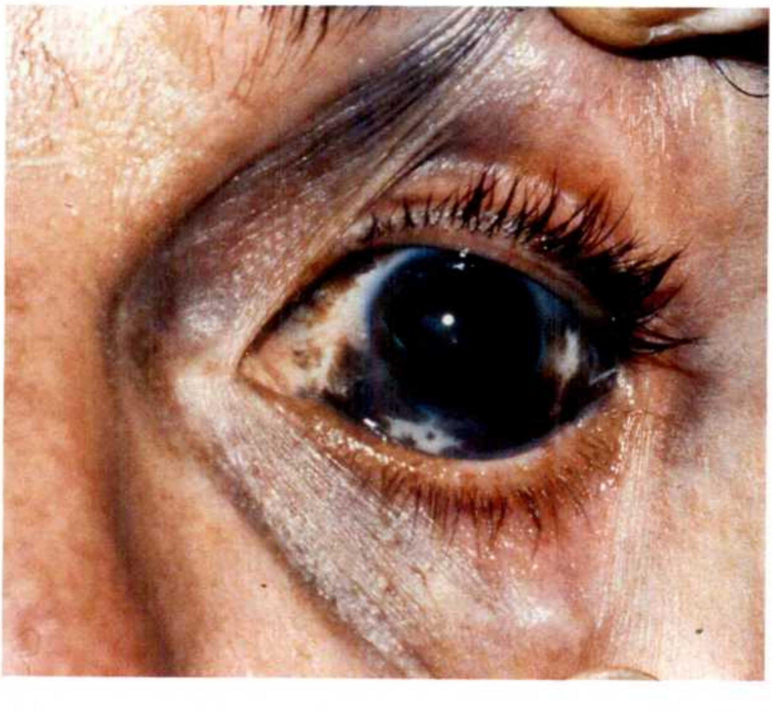
Oculodermal melanocytosis (ODM) or naevus of Ota is a congenital benign melanocytic hyperpigmentation of deep periorbital skin and ocular tissue. The condition is most commonly unilateral and is more frequent in females.[1] Malignant melanomas of the choroid,[2,3] iris,[4] ciliary body,[5] orbit,[6,7] brain,[8] and skin[9] have previously been reported in cases of ODM. We present for the first time a malignant melanoma apparently arising in the optic nerve head of a patient with ODM.

Case report

CLINICAL

A 60-year-old Caucasian man was known to have dark pigmentation of his eye and eyelids since childhood. When he presented to the Tumour Clinic of the Department of Ophthalmology of Ankara Medical School in May 1987 his only complaint was a crescent-shaped dark area in front of his left eye. Visual acuity was 6/9 in this eye. His right eye and eyelids were normal and visual acuity was 6/6. He had ODM involving his left eye and eyelids (Fig 1). In this eye ocular motility and intraocular pressure were normal and there was no proptosis. A relative afferent pupillary defect was detected on the affected side.

Figure 1 Photograph demonstrating oculodermal melanocytosis in the left eye.



On the slit-lamp there were irregular patches of pigmentation in all quadrants of the episclera and the iris was thick and pigmented. Ophthalmoscopic examination revealed a pigmented mass involving the optic disc and extending superonasally in the choroid. Its dimensions were clinically estimated to be 5×3×1 mm (Fig 2). Fluorescein angiography supported the presence of a malignant melanoma (Fig 3).

An orbital computed tomographic (CT) scan demonstrated a well circumscribed tumour of 8 mm in diameter located in the anterior aspect of the optic nerve. The tumour appeared confined to the optic nerve sheath. It extended into the vitreous cavity through the optic nerve head (Fig 4). CT of the head, liver scintigraphy, chest roentgenogram, liver enzyme studies, complete blood count, and urinalysis including melanin and vanillyl mandelic acid were found to be normal.

The patient was informed about the grave situation and enucleation was offered to him but he refused it. He was seen 2 months later in July 1987 and described a rapid loss of vision since his first visit. Visual acuity in his left eye was found to have deteriorated to light perception.

In October 1987, 5 months after presentation, he lost light perception. Ophthalmoscopically the mass had grown in size and extended further into the vitreous. Retinal and preretinal haemorrhages were present on and around the optic nerve head. Some lens opacities were also noted in the left eye. He still refused surgery and did not attend for further appointments.

In January 1989 19 months after presentation the patient returned with a painful glaucomatous and cataractous left eye. Intraocular pressure by applanation was 60 mm Hg and the cornea was oedematous. Further extension of the tumour was suspected and an exenteration of the orbit was performed. Both eyelids were preserved.

PATHOLOGY

Macroscopically the material consisted of the eye and periocular tissues. The eye measured 24×

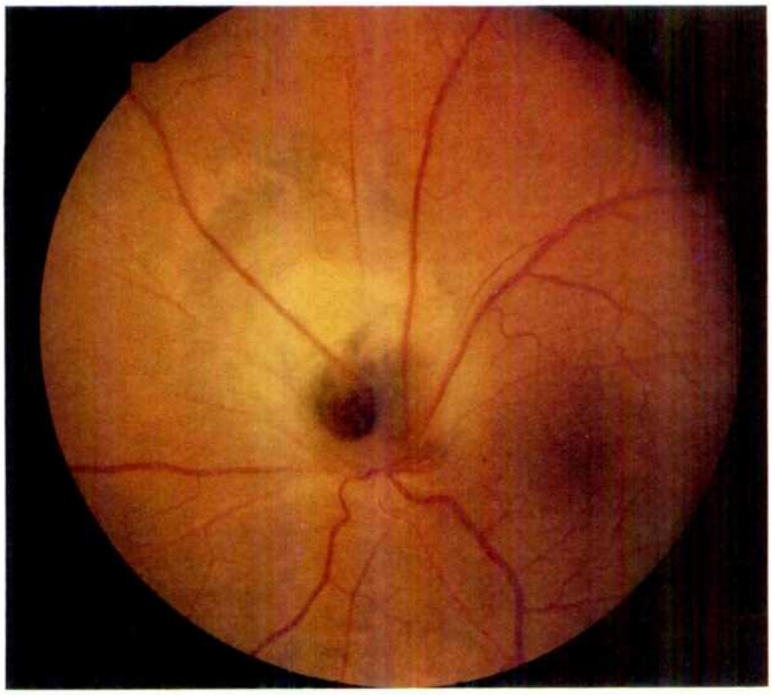


Figure 2 Fundus photograph of the left eye showing pigmented tumour located on the optic disc.

24×24 mm with an 18 mm optic nerve which became detached. The optic nerve was thickened and firm on palpation. It measured 10 mm in diameter anteriorly immediately behind the globe. At this point the tumour infiltrated and replaced the optic nerve and the nerve had become detached from the globe, during manipulation through the plane of soft tumour tissue.

The globe was then sectioned through the meridional plane revealing a mushroom-shaped pigmented tumour mass with diameters 9×7×6 mm extending from the optic disc forwards into the vitreous cavity. The tumour base extended into the choroid 4 mm circumferentially. Pigmented tumour intruded into the meninges of the optic nerve to a point 13 mm from its point of origin on the posterior aspect of the globe (Fig 5). The optic nerve was macroscopically normal at the site of surgical transection.

Upon microscopy the tumour was composed of heavily pigmented epithelioid and plump spindle melanocytes with large numbers of interspersed coarsely pigmented melanophages. The melanoma infiltrated deeply into the nerve head and the subarachnoid space (Fig 6) ensheathing the nerve for much of its length and penetrating the dural sheath forming an extradural mass.

Foci of small bland polyhedral epithelioid and thin spindle naevus cells were present at one anterolateral margin of the intravitreous tumour and within the most anterior part of the optic nerve behind the lamina cribosa suggesting, perhaps, pre-existent naevus. No such foci were present within the tumour extensions into the choroid. Within the anterior chamber there was evidence of melanomalytic glaucoma.

Discussion

Aberrant pigmentation of ODM consists of fusiform or dendritic melanocytes lying in deeper layers of facial skin and globe. The melanocytes normally migrate from the neural crest during embryogenesis and settle superficially in skin and mucous membranes. ODM represents a developmental anomaly in which some melanocytes fail to reach these surface structures.[1 6 10]

These melanocytes which migrate via the distribution of nerves have been demonstrated along ciliary nerves,[7] intrascleral channels,[6] and in orbital tissues.[11] They have also been found in optic nerve leptomeninges[11] and in lamina cribrosa of the optic nerve[12] in eyes with ODM.

Teekhasaenee *et al*[1] reported pigmentation of the optic disc to occur in 23 (18·1%) of their 127 patients with ODM. Gonder *et al*[13] histopathologically demonstrated melanocytes in the optic disc in five (35·7%) of 14 patients with ODM and uveal malignant melanoma.

Malignant transformation of pre-existing melanocytes arrested within the optic nerve or optic nerve head is probable in this case. The bulk of the melanoma was located in the optic nerve. Naevoid elements were also present at this site. A mushroom-shaped tumour mass protruded into the vitreous cavity from the optic disc; peripapillary tumour infiltration into the choroid was limited and symmetrical. It is less likely that the tumour arose in the juxtapapillary choroid.

To ensure complete removal of the tumour exenteration of the orbit was performed. A very long portion of the optic nerve and some periocular tissue was obtained by this procedure.

During the 28-month follow-up period, the patient has regularly attended his appointments and there has been no evidence of tumour recurrence or metastasis.

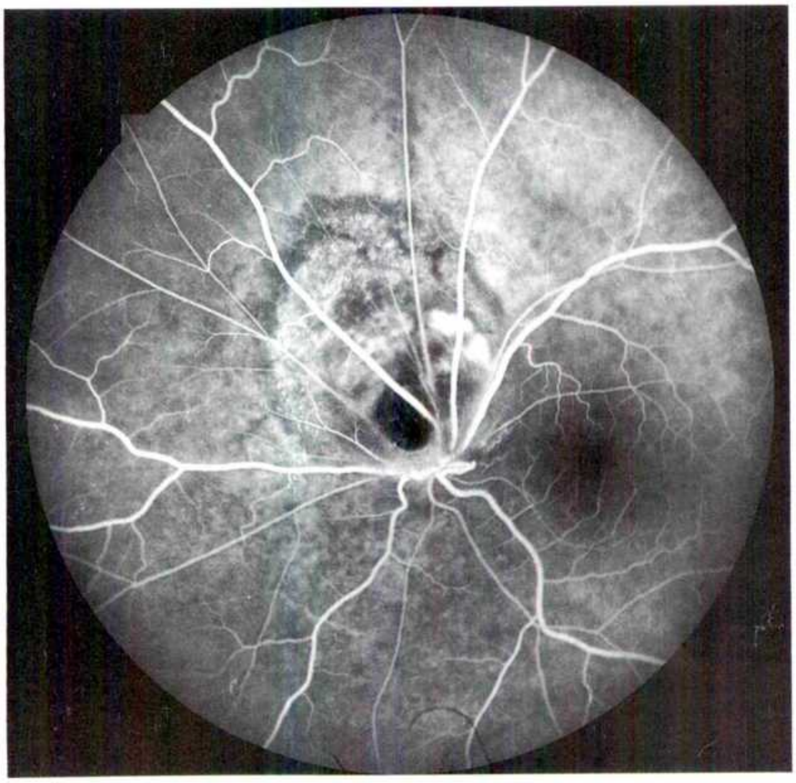


Figure 3 Fluorescein angiogram demonstrates hyperfluorescence of the tumour.

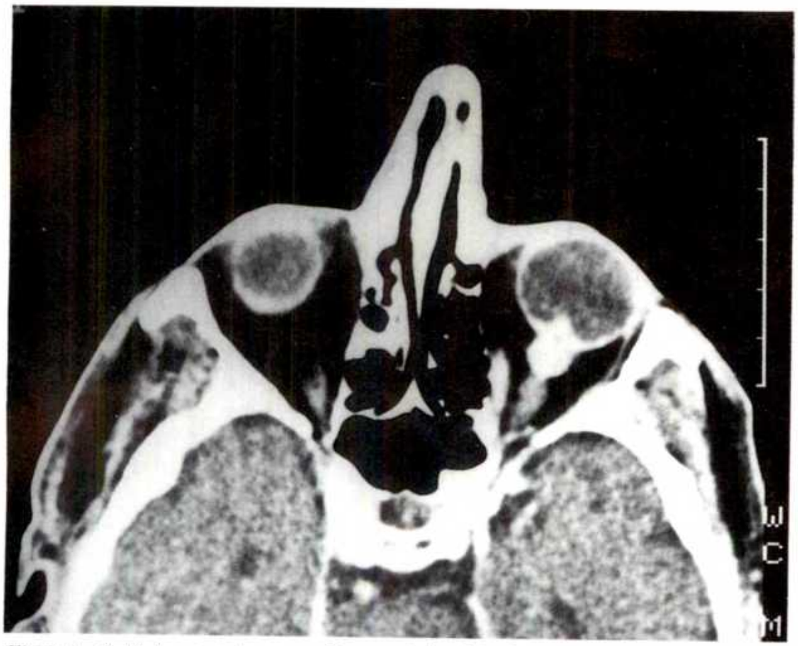


Figure 4 Orbital computed tomographic scan of the orbits showing a tumour located in the anterior portion of the left optic nerve.

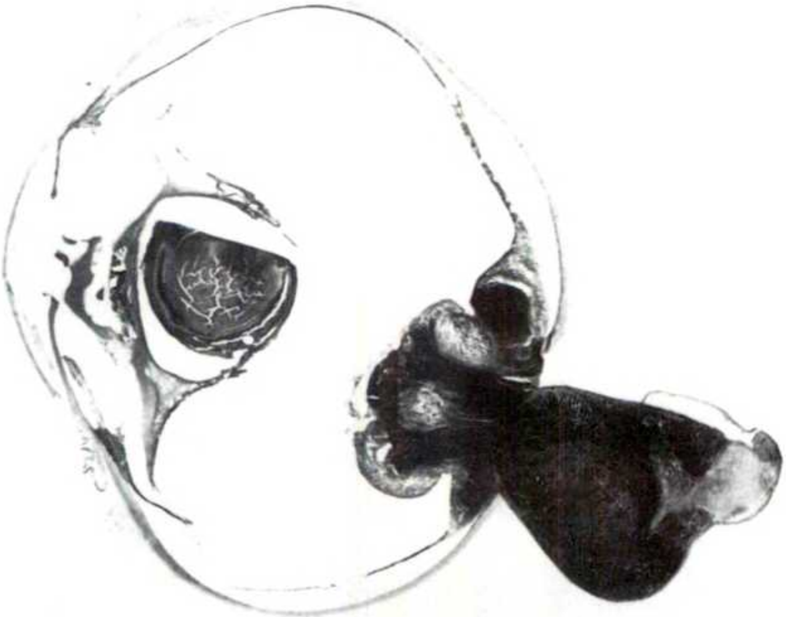


Figure 5 Two separate sections through globe and optic nerve repositioned to reveal tumour in nerve head and subarachnoid sheath. The most posterior portion of the nerve which was clear of tumour is not included (H&E stain).

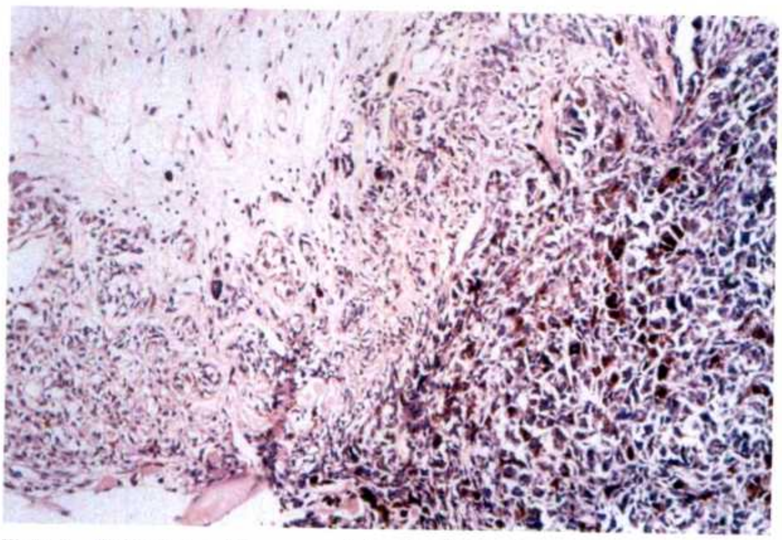


Figure 6 Melanoma involving meningeal sheath and infiltrating optic nerve (H&E stain. Magnification ×70).

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British Journal of Ophthalmology, 1992, 76, 316

Alice in Wonderland syndrome as an initial manifestation of Epstein-Barr virus infection

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Accepted for publication
3 October 1991

Abstract

We present a patient with serologically confirmed Epstein-Barr virus (EBV) infection who had illusions of size, shape, and colour of objects but none of the typical symptoms and signs peculiar to infectious mononucleosis (IM) except sore throat which developed 2 weeks after the initial visual disturbances. The bizarre feelings about the images of body and objects are called the 'Alice in Wonderland syndrome' due to the similarity with Alice's dreams. The same symptomatology including visual metamorphosia is defined in patients with migraine, epilepsy, intoxication due to hallucinogenic drugs, schizophrenia, hyperpyrexia, and cerebral lesions. Alice in Wonderland syndrome has also been reported in the course of IM.

Case report

A 7-year-old girl complained of seeing objects smaller and in different colours than they were, such as seeing her mother's head green and smaller in comparison with her body. These metamorphoses were intermittent lasting a few minutes. She was first examined by an ophthalmologist whose examination including colour vision was completely normal. Neither visual agnosia nor nominal dysphasia was a complaint. However the patient was never examined during an attack, each of which lasted a few minutes. It was thought that she was faking. Her complaints continued and she was admitted to Hacettepe Children's Hospital. Her physical and neurological examinations were normal. Laboratory investigations included a normal brain scan and minimal irregularity of background activity over the posterior areas of the EEG. Estimations of antibodies of types IgG and IgM for EBV were positive by enzymatic immunoassay. The level of IgG antibodies in our patient was 1·2 and that of IgM antibodies was 2·8. During the follow-up period lasting 5 months no other complication occurred and visual symptoms recovered spontaneously. She has been completely normal for 6 months.

There was no personal or family history of epilepsy, migraine, or drug use. The only remarkable information about the family was that her father had had a serologically confirmed hepatitis A infection but our patient was seronegative for HAV.

Discussion

Various neurological and psychological manifestations may occur during or after IM.[1-4] These include meningoencephalitis, encephalitis, the Guillain-Barré syndrome, mononeuritis, personality changes such as irritability, emotionality, asocial behaviour, destructiveness, depression and anxiety, benign recurrent aseptic meningitis (Mollaret's meningitis), inappropriate antidiuretic hormone secretion, myalgic encephalomyelitis syndrome, acute transverse myelopathy, acute cerebellar ataxia, convulsions, and retinochoroiditis.[5-14]

One of the perceptual disturbances in IM is the Alice in Wonderland syndrome. A few cases have been reported after Copperman's first report. Visual metamorphosia was described in patients reported by Copperman[1] as a presenting symptom, but it was realised during the examination that there were other signs suggesting IM, such as generalised lymphadenopathy, splenomegaly, and rash. On the other hand in the patient reported by Sanguineti[2] the length of time elapsing between the initiation of visual symptoms and the development of signs suggesting IM is not known accurately. Since this patient was examined by an ophthalmologist initially it is not known whether she had these other clinical signs at that time. Subsequently Eshel *et al*[3] and Lahat[4] reported two patients with the Alice in Wonderland syndrome which developed after IM.

It is easy to recognise this in a patient with full blown features of IM but this is not so if the visual disturbances preceded the classic symptoms of IM or if IM follows a subclinical course. When our patient suffered from micropsia there was no other sign suggesting IM.

This patient is another example of the extensive variation of the presenting symptoms of IM reminding us to keep the Alice in Wonderland syndrome in mind in patients with visual illusions but no other symptoms.

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LETTERS TO THE EDITOR

Laser card

SIR,—The management of diabetic patients in a large teaching hospital presents the medical and clerical staff with considerable logistical difficulties.

Many diabetic patients have to attend different specialist clinics: physicians, ophthalmic, renal, diabetic, foot, etc. The frequency of their visits to other departments such as the antenatal clinic may also be influenced by diabetes related problems. It can be a challenge to ensure that the medical records will be available at each and every visit. This might involve chasing sets of notes in various offices, clinics, and wards, sometimes located on more than one site. Furthermore, some departments like the renal unit may be understandably reluctant to release the records of patients due to have dialysis or awaiting transplants. The diabetic department at our hospital has found it useful to have its own records. However, this entails having a separate filing system. It would clearly be impracticable for each department to do the same; moreover this would cause a major breakdown of communication between the various specialists looking after a patient.

It is not surprising therefore that the phenomenon of 'missing notes' is commoner in teaching hospitals.[1] This leads to significant clinical difficulties and can affect patients' confidence in the system or the treatment. It also has a detrimental effect on auditing.[2]

The proper management and follow-up of diabetic retinopathy depends to a large extent on the availability of well documented medical records. In view of the limited time and number of ophthalmologists, and because the laser unit is located on the ward rather than in the outpatient department, it is not possible to perform laser treatment during clinic time. This is done in parallel with theatre sessions. The inevitable increase in number of patient attendances is associated with a higher incidence of missing records. This is further complicated by the possibility of entering clinical and treatment details in general, diabetic, or temporary sets of notes. No full and complete sequence will be available in any such record. This lack of continuity may have serious clinical and medicolegal implications.

The suggestion that each patient could hold his own record is attractive but can be achieved only if and when all records are computerised; otherwise it would involve a considerable amount of duplication. However, a simple compromise between such a system and the present one can be reached. We have designed a laser card (Figs 1 and 2) which is issued to every patient who requires laser treatment. It serves the purpose of an appointment card and provides the patient and the attending nurse with some useful information. More importantly, space is available in order to enter the treatment indicated (eg, focal above fovea, panretinal photo-coagulation (PRP), as well as details of the treatment performed. Diabetic patients are quite used to holding treatment cards and should have no problem handling the laser card.

In our experience the laser card has proved to be particularly useful when medical records are missing but it is also a convenient way to find out, at a glance, the total amount of treatment each eye has received. This can be helpful in prospective or retrospective studies which would otherwise be undermined by missing notes. The application of a similar system to various clinical practices could contribute to making data easily available for auditing.

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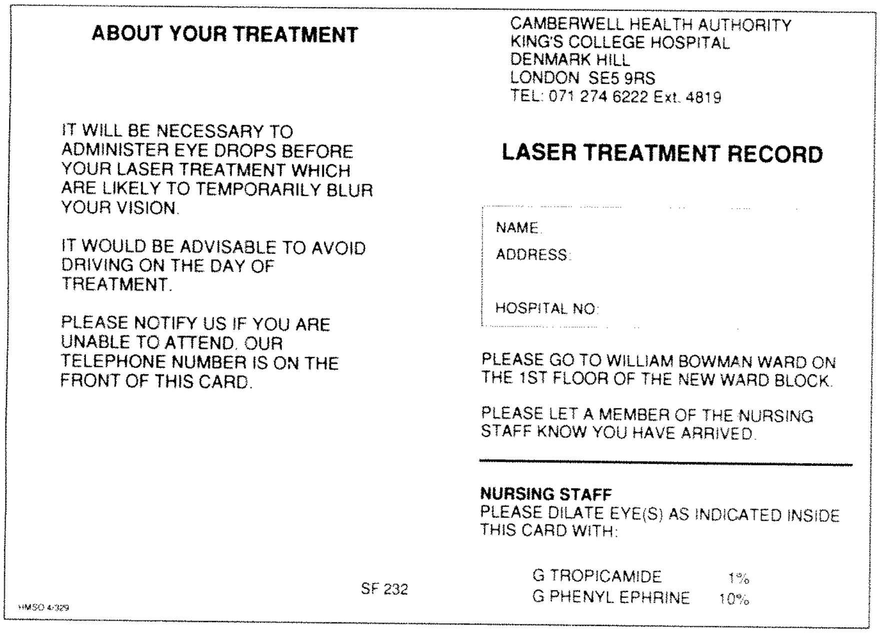

ABOUT YOUR TREATMENT

IT WILL BE NECESSARY TO ADMINISTER EYE DROPS BEFORE YOUR LASER TREATMENT WHICH ARE LIKELY TO TEMPORARILY BLUR YOUR VISION.

IT WOULD BE ADVISABLE TO AVOID DRIVING ON THE DAY OF TREATMENT.

PLEASE NOTIFY US IF YOU ARE UNABLE TO ATTEND. OUR TELEPHONE NUMBER IS ON THE FRONT OF THIS CARD.

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CAMBERWELL HEALTH AUTHORITY
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LASER TREATMENT RECORD

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ADDRESS

HOSPITAL NO

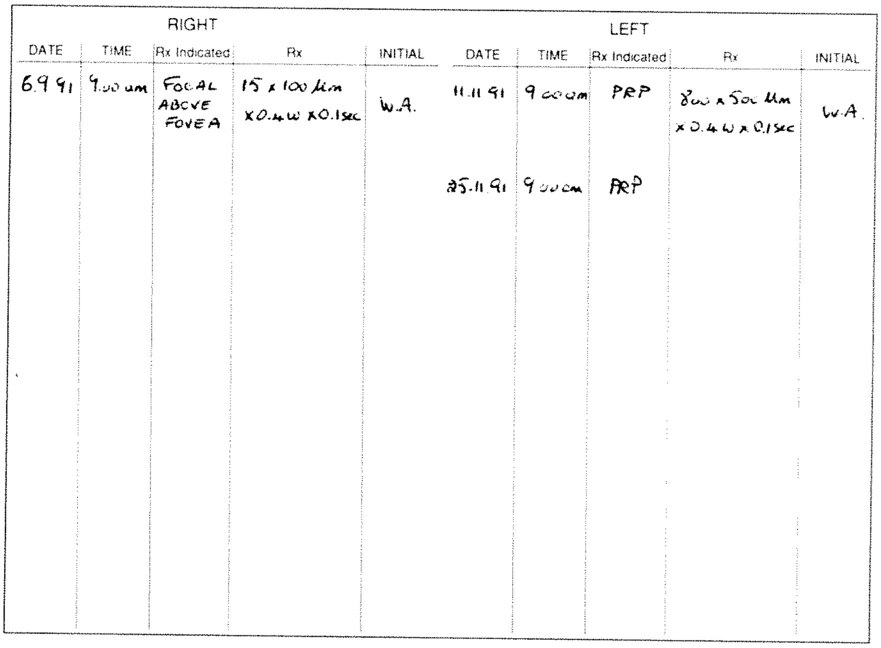
PLEASE GO TO WILLIAM BOWMAN WARD ON THE 1ST FLOOR OF THE NEW WARD BLOCK.

PLEASE LET A MEMBER OF THE NURSING STAFF KNOW YOU HAVE ARRIVED.

NURSING STAFF
PLEASE DILATE EYE(S) AS INDICATED INSIDE THIS CARD WITH:

G TROPICAMIDE 1%
G PHENYL EPHRINE 10%

Figure 1 Laser treatment card.



RIGHT					LEFT				
DATE	TIME	Rx Indicated	Rx	INITIAL	DATE	TIME	Rx Indicated	Rx	INITIAL
6.9.91	9.00 am	FOCAL ABOVE FOVEA	15 x 100 µm x 0.4 W x 0.1 sec	W.A.	11.11.91	9.00 am	PRP	800 x 500 µm x 0.4 W x 0.1 sec	W.A.
					25.11.91	9.00 am	PRP		

Figure 2 Reverse of card indicating treatment given.

Delayed ciliochoroidal detachment following intraocular lens implantation

SIR,—We read with interest the recent article by Dawidek *et al*.[1] The authors suggest that the ciliochoroidal detachment in their cases was due to ciliary sulcus fixation of the implant. We reported[2] hypotony and ciliochoroidal detachment following uneventful phacoemulsification due to traction on ciliary processes adherent to the posterior capsule and lens remnants. Surgical capsulotomy cured the ciliochoroidal detachment. Magruder *et al*[3] confirmed our observation. They reported a case of ciliochoroidal detachment that occurred after extracapsular cataract extraction with posterior chamber intraocular lens implantation which was cured by Nd:YAG laser capsulotomy. These two cases support the concept of ciliary body traction by the posterior capsule as a cause of ciliochoroidal detachment. Unfortunately the authors did not mention the status of the posterior capsule in their patients. We believe that capsulotomy should be considered in cases of ciliochoroidal detachment following extracapsular cataract extraction. Removal of the implant as suggested by the authors is probably unnecessary.

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1 Dawidek GMB, Kinsella FM, Pyott A, Hughes DS, Kyle PM, Lane CM. Delayed ciliochoroidal detachment following intraocular lens implantation. *Br J Ophthalmol* 1991; 75: 572–4.
2 Geyer O, Godel V, Lazar M. Hypotony as a late complication of extracapsular cataract extraction. *Am J Ophthalmol* 1983; 96: 112–3.
3 Magruder GB, Harbin TS. Ciliochoroidal detachment associated with stretched ciliary processes. *Am J Ophthalmol* 1989; 106: 357–8.

Reply

SIR,—We wish to thank Geyer and Lazar for kindly pointing out a further possible cause of late ciliochoroidal detachment following extracapsular cataract extraction. In their case and that reported by Magruder and Harbin a peripheral iridectomy was performed which allowed subsequent visualisation of the ciliary processes in that area. With our three cases, although the posterior capsules were all intact, none had a peripheral iridectomy. It was not possible, therefore, to see if ciliary process traction were present. However, the posterior capsule was flaccid, and this suggests that traction was not significant. Furthermore, our three cases all responded briskly to high dose oral steroids. Neither oral nor topical steroids could be expected to relieve ciliary process traction. The resolution of the ciliochoroidal detachment in all three cases following drug treatment strongly suggests that persisting ocular inflammation and altered permeability of the blood aqueous barrier were present. These could be due to ciliary sulcus fixation of the implant. Although posterior capsulotomy cured the ciliochoroidal detachment in the two cases described in the above letter, it is worth considering that capsulotomy itself may be complicated by cystoid macular oedema and retinal detachment.

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Optic foraminal radiography – a redundant investigation?

SIR,—The paper by Kincaid and Dutton[1] illustrates an example of medical practices which are passed on, almost anecdotally, for many years without there being any hard evidence to support them.[2] Undoubtedly optic foramen views *can* show evidence of glioma, meningioma, etc where these exist but to conclude that they are therefore worth doing routinely is illogical.

A fair proportion of medical practice can be shown to be based on unsound logic. Another example is Professor Eddys' discovery that the established treatment of glaucoma had been passed down through the generations since 1906 without any controlled trials ever being done to support it.

The authors are to be congratulated on pointing out the inefficiency of routine optic foramen views and on the consequent saving of resources and the reduction in radiation dose to future patients.

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Sheffield*

1 Kincaid, W, Dutton GN. Optic foraminal radiography — a redundant investigation? *Br J Ophthalmol* 1991; 75: 665–6.
2 Smith R. Where is the wisdom. . . ? The poverty of medical evidence. *BMJ* 1991; 303: 798–9.

Installing a database for the retrieval of fluorescein angiograms

SIR,—We have developed a computerised database filing system for the storage and retrieval of fluorescein angiogram records. This was achieved by harnessing a novel coding and classification system to a frequently used database program. The system was devised to replace the manual punch card filing system for fluorescein angiograms 7 years ago. It was originally written for an Apricot Personal Computer, using the dBase II software package and has now been modified to run on an IBM 386 compatible hard disc computer running dBase 3+, but it remains downwardly compatible with all MSDOS computers. The use of current classification systems[1-3] was entertained but rejected because of lack of detail. Fortunately this allowed us to structure the database according to our specific requirements, which included:

(1) A new four-section request and report form.

(2) A new coding structure to meet the future research and data retrieval requirements.

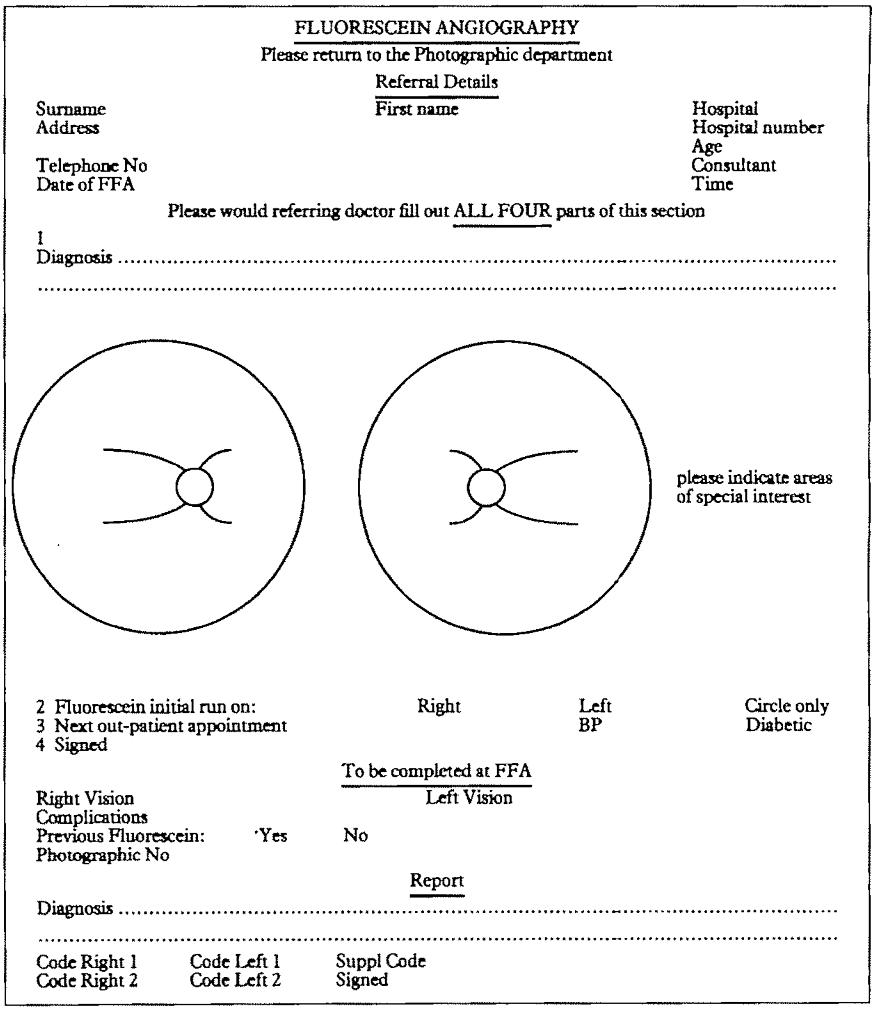
(3) Computerised storage of patient and consultant details.

(4) A user-friendly system allowing data access without prior computer knowledge, rapid and simple data entry.

(5) A multiple layer data security system.

The request and report form was drawn up to enable the medical photography department (Fig 1) to ascertain the indications and special features to be assessed with angiography. It has the additional benefit of allowing the doctor to write the report without the need to refer back to the patient's records. Specific photographic problems and details are recorded, and the report is summarised and coded for computer data entry. After the angiogram is entered into the database the form is then stored with the angiogram for security.

The success of a database is ultimately dependent on its ease of use. The tedious and time-consuming parts of database use are data input, and a system had to be developed which matched this task with the training and motivation of the staff available. The two fundamental questions to be answered were whether or not to code and how much information to record.[4,5] Coding is helpful in that it eliminates the problems caused by synonyms in medical terminology. This saves time, because a non-coded system requires to be extensively validated at the time of data entry. Coding has the further advantage of enabling data to be easily classified. Each digit is used in a hierarchical fashion in which the first digit describes the general entity, while each succeeding digit specifies greater detail. We decided to limit the codes to diagnosis only rather than break down the data into further detail. This uniaxial approach would satisfy the requirements of simplifying data input and note retrieval, but would preclude a more detailed analysis on the basis of data contained in the



FLUORESCEIN ANGIOGRAPHY
Please return to the Photographic department
Referral Details

Surname
Address
First name
Hospital
Hospital number
Age
Telephone No
Consultant
Date of FFA
Time

Please would referring doctor fill out ALL FOUR parts of this section

1
Diagnosis ....
....

please indicate areas of special interest

2 Fluorescein initial run on: Right Left Circle only
3 Next out-patient appointment BP Diabetic
4 Signed

To be completed at FFA

Right Vision
Left Vision
Complications
Previous Fluorescein: Yes No
Photographic No

Report

Diagnosis ....
....

Code Right 1 Code Left 1 Suppl Code
Code Right 2 Code Left 2 Signed

Figure 1 Form used for requesting and reporting on fluorescein angiograms.

0000–0999	Vascular
1000–1999	Diabetes
2000–2999	Inflammatory Retinal/Choroidal Disease
3000–3999	Primary Macula
4000–4999	Retinal Degeneration
5000–5999	Primary Haematological
6000–6999	Optic Disc
7000–7999	Miscellaneous
8000–8999	Tumours
9999	Normal

Figure 2 First page of the coding handbook showing the broad classification.

Fluorescein Database

OPENING MENU

1. Update records
2. Find record by name
3. Find patients by diagnostic code
4. Display patient record
5. Edit patient record
6. Back-up database to floppy disc
0. Terminate session

press a number 0 to 6

Figure 4 The opening menu for data input and output.

computer. It nevertheless satisfied the important objective of reducing time spent in front of a terminal and preventing the frustration of inputing potentially redundant information.

The four-digit coding structure was devised by RW and based around a combination of pathological and anatomical parameters and heavily weighted in numbers variables towards the common conditions. The first digit covers the broad area (Fig 2), with increasing layers of subdivision within the next three digits (Fig 3). Codes from 7000 to 7999 are used for conditions that do not logically fall elsewhere in the classification system, with 70– specifying trauma. Increasing detail is imparted by the third figure; 7020, for example, codes for commotio retinae. In this case the fourth figure is not used, indicating that the system is flexible enough to permit expansion. Currently only integers are used, but the system is designed to use letters at any of the four positions, allowing for a massive increase in coding possibilities. The patient is allocated two 4-digit codes to each eye with a supplementary code available if necessary. This solves the potential problem that arises when the broad divisions overlap. For example, optic disc swelling in diabetes mellitus would be given the codes 1000 and 6140. Visual acuity, laser treatment, and the consultant's name are entered as codes: other details are entered directly. The patient display page in the program will decode the demographic details but currently not the diagnostic codes, though these are soon to be incorporated. The report is dictated and a code assigned by the doctor from a 12 page handbook without the need to access the computer. Data entry is carried out by the secretary using a menu-assisted program (Fig 4). No knowledge of the basic dBase programming language is required. After data entry, specific details of each patient are printed out, together with the allocated record numbers. These hard copy details are then filed separately. The operator is prompted to back-up the file to a floppy disc, in a 3-disc rotation system, and intermittently a further floppy disc copy is taken for archiving. Initially, early operator errors allowed some data loss, but this was rapidly retrieved from the backup and hard copy details.

2597 fluorescein angiograms have now been entered into the database over the last 6 years creating a master file of 336 622 bytes. The increasing file size has benefited from the increasing power of the computer hardware, which is directly connected to a printer for the hard copy. In the early stages the smaller computer was perfectly adequate for the modest file size, but it would be tediously slow at this stage.

The fluorescein database has improved access to angiogram records, especially for research, teaching, and medical audit. Quantitative analysis relating to diagnosis, age, time period, and consultant is easily achieved. More specific analysis has benefited from the completeness and speed of the diagnosis-based medical search. The codes themselves have helped to standardise the reports, by forcing comment, for example, of the severity of eschaemia in retinal artery occlusion. The structured approach has benefited the photographer in conveying the important clinical features to be picked up during angiography. It has also facilitated data entry for the secretary.

The acceptability and usefulness of this program are reflected in its long track record, its having been in use at our hospital for 7 years. The program and handbook have already been made generally available and are currently used in many ophthalmology units throughout the country. Interested parties are asked only to pay the cost of the magnetic media and postal charges. The minimum computer requirement is a hard disc, single floppy IBM PC compatible computer, with the dBase II or dBase 3+ program and any style of printer.

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R WILSON
R MARSH
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1 World Health Organisation, International classification of diseases. 9th revision. Geneva: World Health Organisation, 1977.
2 Systematized Nomenclature of Medicine (SNOMED). 2nd ed. Skokie IL, College of American Pathologists, 1979.
3 Côté RA, Robboy S. Progress in medical information management systematized nomenclature of medicine (SNOMED). *JAMA* 1980; 243: 756–62.
4 Benson T. Dawn of a third era. *Health Service Journal* 1990; 600–1.
5 Earlam R. Körner, nomenclature, and SNOMED. *BMJ* 1988; 296: 903–5.

MISCELLANEOUS 7000–7999

- 7000 Trauma
  - 7010 Choroidal Rupture
  - 7020 Commotio Retinae
  - 7030 Intraocular Foreign Body
- 7100 Retinal Detachment
  - 7100 Rhegmatogenous detachment
  - 7110 Traction detachment – please also code as to cause
  - 7120 Exudative retinal detachment
  - 7130 Retinoschisis
  - 7140 Retinal cyst
- 7200 Angioid Streaks
  - 7200 Pseudoxanthoma elasticum
  - 7210 Paget's Disease
  - 7220 Ehler-Danlos
  - 7230 Sickle Cell – please also code under haematological
  - 7240 Other
    - 0–uncomplicated
    - 1–with disciform lesion
- 7300 Ocular albinism
- 7400 Myopic degeneration
- 7500 Choroidal folds
- 7600 Coloboma
- 7700 Vitreous abnormalities

Figure 3 A sample page from the coding handbook.

BOOK REVIEWS

Case Presentations in Medical Ophthalmology. By Jack J Kanski, Teifi E James. Pp 116. £14.95. Butterworth-Heinemann: Oxford, 1991.

This book is primarily aimed at doctors preparing for membership of the Royal College of Physicians.

It begins with a short but nevertheless excellent introduction containing instructions on how to examine a short case, which can be applied to all specialties and all examinations.

This small paperback contains 50 short case presentations with clinical photographs and three questions on each case. One further photograph and full answers are to be found at the back of the book.

The illustrations are excellent (as is to be expected from Mr J Kanski) and the questions are well thought out.

Unfortunately a few answers are lacking in advice: for example a painful third nerve palsy is not listed as a potential medical emergency; the importance of examining the other cranial nerves and the palate and nasopharynx in a diabetic patient with a VIth nerve palsy is not emphasised; and a case of retrobulbar neuritis is described when the visual loss is painless, which should alert the physician to alternative diagnoses.

However, despite these few reservations the book is beautifully presented, simple to understand, and would undoubtedly help all aspiring physicians and ophthalmologists as well as junior doctors from other specialties both to pass examinations and to practice safe efficient medicine.

L HOWE
E GRAHAM

Scanning Laser Ophthalmoscopy and Tomography. Eds J E Nasemann, R O W Burk. Pp 272. £64. Quintessenz: New Malden, Surrey, 1990.

This emerging technology represents a significant advance in recording fundus appearances. Lower light levels are required than in conventional ophthalmoscopy and fundus photography. Good resolution, both spatial and temporal, is attained and in the confocal mode a promising degree of three dimensional information can be obtained. In the vast majority of cases dilatation of the pupil is not required. As yet the field of view is limited and since the imaging is digital the transversal (two-dimensional) resolution decreases as the field is enlarged, limited by the pixel (picture points) capacity of the computer and video systems.

Tomography, in which a series of confocal images (typically 32) is recorded, each advancing a small distance axially (typically 50 μm), then analysed to find the point of maximum intensity, has been applied particularly to the analysis of the normal and diseased optic disc and macula. A number of uncertainties still exist in the interpretation of these data but the accuracy and reproducibility of optic disc measurements compares favourably with other methods. The cornea and anterior segment can also be investigated in this mode.

This book is a presentation of 26 papers, all of high technical quality given at the first international symposium on scanning laser ophthalmoscopy and tomography held in Munich in 1989. The opening papers deal with the principles of scanning laser ophthalmoscopy and an overview of its applications, followed by detailed accounts of angiography, retinal circulation time estimation, linear blood flow estimation, fundus reflectometry, static perimetry, and eye movement measurement. The remaining 12 papers deal with tomography; it is worth reading the last three first to gain a good technical insight.

The book is strongly recommended to all ophthalmologists who wish to keep abreast of this important technique which is bound to have a significant impact in the future. Though representing a heavy capital investment, its potentiality and diversity of application should ensure it a place in future clinical instrumentation.

D W HILL

Eyelid Surgery. By J Earl Rathbun. Pp. 290. £95.00. Little, Brown: London, 1991.

This new book is a practical manual based on the author's wealth of personal experience. J Earl Rathbun who is in practice in San Francisco has made a considerable contribution to ophthalmic plastic surgery through his teaching and publications over many years. In this book he presents his preferred techniques for a wide spectrum of eyelid surgery; surgery of the socket is not included. The book assumes little prior knowledge of the subspecialty. Whether describing the anatomy, discussing a classification, or explaining the steps of an operation the text is clear, easy to read, and well-illustrated with clinical and operative photographs supported by line diagrams. The book as a whole is well planned and easy to use. The index is comprehensive and each chapter has a concise list of up-to-date references.

Criticisms are minor. Some of the operative series in black and white are less clear than those in colour; the description of partial thickness skin flaps might have been included with eyelid and canthal reconstruction rather than basic techniques; the chapter on cicatricial entropion and trichiasis does not cover the treatment of distichiasis in any detail; and the inclusion of a chapter on socket surgery would have been useful.

The book is a pleasure to read. It is likely to appeal mainly to those starting ophthalmic plastic surgery but it would be a valuable addition to any ophthalmic library.

A G TYERS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express), stating card number, expiry date, and full name.

NOTES

European Association for the Study of Eye Complications in Diabetes (EASDEC)

The second meeting of this association will be held in Baden near Vienna, Austria on 5–6 September 1992 prior to the EASD meeting in Prague. The meeting will be run in workshop style and therefore only 100 active participants – in order of application – will be accepted. The topics discussed will be 'Hypertension and diabetic retinopathy', and 'The role of the vitreous in diabetic retinopathy'. Abstracts are invited to reach the organisers by 30 June 1992. Further details from: Professor E M Kohner, President, EASDEC, Diabetic Retinopathy Unit, Department of Medicine, Royal Postgraduate Medical School, Du Cane Road, London W12 0NN, UK *or* Docteur B Cathelineau, Secretary, EASDEC, Unite d'Ophtalmo Diabetoloie, Hopital Saint Louis, 1 rue Claude Vellefaux, 75475 Paris, Cedex 10, France.

Retinal Detachment Surgery

A basic course on retinal detachment surgery (with panel discussion by European and North American Faculty as well as case presentations) will be held on 23–24 May 1992 at the Brussels International Conference Centre. The theme will be 'Minimal detachment surgery with segmental buckling and non-drainage'. Further details: Congress Office, Professor Dr I Kreissig, Universitäts-Augenklinik Abt III, Schleichstrasse 12, D-7400 Tübingen, Germany. (Tel: 07071-293741. Fax: 07071-293730.)

Glaucoma Group

David Cole Travel Fellowship
The David Cole Travel Fellowship, instituted by Merck Sharp & Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1992. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

Glaucoma Group Research Grant
The Glaucoma group research grant, sponsored by the International Glaucoma Association will be available for a research project clinically orientated to glaucoma for 1992. The award will be equivalent to £2500. The grant may be used towards salary or project expenses or for buying equipment.

Glaucoma Group Research Award
The Glaucoma group research award, sponsored by Alcon Laboratories will be given in support of a research project related to glaucoma. The award will be equivalent to £2000.

These awards are available to both medical graduates and non medical scientists resident in the United Kingdom or Ireland. They may be held concurrently with other awards.

For further details: Dr S Nagasubramanaian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK. The closing date for applications is the 30 June 1992. The successful candidate will be informed by August 1992.

International Journal of Sports Vision

The first issue of the *International Journal of Sports Vision* (IJSV) will be published in May 1992. For more information, contact either: Dr Darlene A Kluka, Co-Editor *International Journal of Sports Vision*, The University of Alabama at Birmingham, 117 Education Building, UAB Station, Birmingham, AL 35294-1250, USA (Fax: (205) 934-4963) or Dr Joseph N Trachtman, OD, Co-Editor, *International Journal of Sports Vision*, Institute for Advanced Vision Technology, 26 Schermerhorn Street, Brooklyn Heights, NY 11201, USA. (Fax: (718) 237-1454.) Papers are invited.

Correction

The following corrections should be made to the paper published by BenEzra *et al* (*Br J Ophthalmol* 1990; **74**: 350–2). The units for CsA levels in the figures should be μg/l as expressed in the text and *not* μg/ml.

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Second class postage paid, Rahway, NJ. Postmaster: send address changes to: *British Journal of Ophthalmology*, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

ISSN 0007-1161.

Published by British
Medical Association,
Tavistock Square, London
WC1H 9JR.
Typeset by
Bedford Typesetters Ltd
Printed by
Centurion Press Ltd

British Journal of Ophthalmology, 1992, 76, 321

BRITISH JOURNAL OF
OPHTHALMOLOGY

Editorial

Cataract management

The changes which have taken place in cataract management over the past 20 years are profound but are by no means complete. This issue sees the publication of a survey of current practice in cataract management, for both surgery and anaesthesia, by Hodgkins *et al* using data obtained from consultants in England and Wales during the first half of 1991.

Such a survey provides a useful source of information about what is going on across the country so far as this ophthalmic 'bread and butter' activity is concerned. In addition, it allows each of us a glimpse of how our own clinical values and actions match with those of our colleagues. No laurels are awarded but there is hopefully some spur to those of us who might be thought to be lagging behind and so depriving themselves and their patients of widely agreed advantages.

There are, necessarily, many questions left unanswered. The design of surveys of this kind is a balancing act between the amount of information obtainable and the rate of effective cooperation by the contributors. A return rate on this occasion of 86% must be considered creditable, but at the expense of all sorts of other things it may have been useful to know. Nevertheless, interesting matters are brought to light and bear further discussion.

Extracapsular surgery is now the norm. Any lingering idea that such techniques could be mastered only after a thorough grounding in intracapsular surgery has clearly been abandoned. That even a small number of surgeons continue positively to favour intracapsular surgery and do not consider intraocular lens implantation as routine is a surprise. One wonders how they are able to resist the pressure of patient demands quite apart from being able to reject (assuming they have considered) the copious evidence in favour of alternatives.

A similar small number of contributors are found on 'the frontier' with only 2% practising phacoemulsification despite, as the authors point out, the availability of the techniques for many years. Judging by the popularity of the well filled courses on this subject over the last 18 months I predict the emergence of a different picture at the next survey. This is not the place to consider the merits of small incision techniques, but I suspect they will prove irresistible.

The authors of this survey report have concentrated particularly on the role of anaesthesia in cataract management. Despite the fact that local anaesthesia was used frequently by only one fifth of their respondents, the burden of discussion has fallen so heavily on this subject one cannot escape the conclusion that the authors are using their findings willy nilly to grind an axe of their own devising. Wong and Steele, with their survey in 1985,[1] did much the same with regard to extracapsular surgery and it will be interesting to see whether time will reward these authors in a similar manner. The issues, however, are not so straight forward.

General anaesthesia continues to enjoy some inherent advantages for the cataract surgeon – guaranteed akinesia and peroperative control of ocular physiology for instance. Besides, general anaesthesia is making advances of its own with the introduction, for example, of laryngeal masks and relaxing agents from which patients can enjoy an almost instantaneous recovery. In our own hospital both local and general anaesthesia are deemed suitable for the management of day cases. These two issues must now be separated for consideration of their advantages in patient management. Local anaesthesia must stand or fall on its own value in assisting the surgeon to achieve the desired clinical outcome.

There are yet more complicating factors which have to be considered. Patients can succumb to the exigencies of local anaesthesia, particularly if it is a technique reserved for the least fit, or accompanied by the administration of intravenous sedation. Regulations now advocated by the Association of Anaesthetists involve the introduction of a measure of supervision and monitoring, not only during the surgery but from the start of the administration of the anaesthetic, be it local or general. Such arrangements will have, as yet, uncalculated cost implications. Surgeons will not be in a position to resist these developments, designed as they are for the greater safeguard of the patient, without exposing themselves to the risk of accusations of impropriety, or even professional negligence. The days when ocular local anaesthesia can remain the exclusive province of the ophthalmologists are numbered. The interest of our anaesthetic colleagues in this field really needs to be welcomed rather than resisted.

Speed and costs were considered relatively unimportant by the respondents to this questionnaire. They are, however, very important having a direct bearing on the efficient use of resources. Reorganisation of the National Health Service with its emphasis on fiscal matters, together with the introduction of regular audit, will combine to lift the profile of these factors and their influence on our activities. Failure to appreciate this may carry heavy penalties.

These surveys reveal a fascinating spectrum of clinical behaviour and attitudes with aggressive pioneering at one end and seemingly willful intransigence at the other. I look forward to the next analysis of this subject with great interest, but not, please, for several more years.

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British Journal of Ophthalmology, 1992, 76, 322

Editorial

The sensitive period in infancy

When a child is born with a truly congenital squint or a unilateral barrier to vision one expects that the patient will swiftly develop dense amblyopia and fail to develop binocular function. This situation has been simulated in animal experiments and much has been written on changes, both structural and functional, in the retina, lateral geniculate nucleus, and visual cortex.

In this context, the paper by Elston and Timms, in this issue, is of great interest in that it points out that the newborn infant is relatively resistant to amblyopia in the first few weeks of extrauterine life. They report seven neonates with either congenital sixth nerve palsy (four cases), congenital third nerve palsy (one case), retinal haemorrhage, or lid haematoma (one case each). In all cases the motor or sensory disruption would have been adequate to produce amblyopia if the problem had persisted, but spontaneous resolution occurred in all cases and on subsequent examination at ages ranging between 10 months and 5 years all patients had normal findings on orthoptic examination.

Elston and Timms rightly draw attention to the period required for the sensorimotor obstruction to disappear. In their series this was from 4 to 6 weeks, and they therefore conclude that the latent period is at least this long. They are unable to state from their study what the upper limit of this period is and whether it is identical for the development of amblyopia and for development of binocular single vision.

Further careful observations of otherwise normal neonates with early ocular problems will be required to help define the limits of the latent and sensitive periods. In this context one should note the recent report by Cheng *et al*[1] on visual results after surgery for monocular congenital cataract, which found that the cases with good visual results were exclusively those whose visual rehabilitation had been achieved by 17 weeks of age.

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British Journal of Ophthalmology, 1992, 76, 323–326

ORIGINAL ARTICLES

Current practice of cataract extraction and anaesthesia

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Abstract

A questionnaire regarding preferred methods of cataract extraction and anaesthesia was sent to 456 consultant ophthalmologists in England and Wales. Replies were received from 86% (n=392), 83% (n=380) having completed the questionnaire in full. The most frequently employed surgical approach was non-automated extracapsular cataract extraction. Only 2% of surgeons (n=8) used phacoemulsification routinely and 2% (n=7) used intracapsular extraction. Intraocular lens implantation was the standard practice of 99% of surgeons (n=376). There has been a dramatic increase in the popularity of local anaesthesia, which was employed routinely (in more than three-quarters of their cases) by 20% of surgeons (n=76). Retrobulbar infiltration remains the most common method of administration. Sedation was given routinely by 45% of surgeons (n=171) when using local anaesthesia. Medical contraindications and patient preference were considered the most important reasons for selecting local anaesthesia rather than general. The exclusive use of general anaesthesia in cataract surgery appears to be diminishing.

Cataract extraction is one of the most commonly performed operations in this country but has undergone considerable change in the last 20 years. Despite its increasing frequency,[1] waiting lists remain long. There is inevitably, pressure on the surgeon to provide the most beneficial, efficient, and cost effective procedure available. A diversity of operative and anaesthetic techniques exists. Current discussion in the ophthalmic literature suggests an increased interest in local anaesthesia,[2-4] day case surgery,[5] and phacoemulsification.[6] Almost all cataract extractions are performed under local anaesthesia in the USA, where the hospital stay rarely exceeds 2 hours.[7] The practice of retrobulbar infiltration has been questioned.[8-10] Peribulbar anaesthetic techniques[11] and other alternatives[12 13] have been suggested.

Local anaesthesia provides a number of advantages over general. There are fewer metabolic changes[14] and, in particular, a reduction in systemic complications such as postoperative confusion, postural hypotension, and vomiting.[15] It allows earlier mobilisation, which is especially desirable in an elderly population and has facilitated the development of day case surgery.[16] Cost effectiveness[5] and popularity with patients[17] have been established.

We thought it timely to undertake a national survey to document current surgical practice in England and Wales in terms of operative and anaesthetic techniques.

Material and methods

A questionnaire was sent to every consultant ophthalmologist in England and Wales, the names and addresses having being obtained from the College of Ophthalmologists. It contained questions designed to elicit the preferred techniques of cataract extraction and anaesthesia. The following subjects were covered: routine method of cataract extraction; frequency of use of local anaesthesia; the use of sedation with local anaesthesia; indications for local anaesthesia; indications for general anaesthesia. Questions, detailed in Tables 1–8, were brief and limited to one side of A4 paper to encourage completion.

To assess the reasons for preferring either local or general anaesthesia a number of possible indications were suggested. Consultants were asked to state, in order of importance, indications for the selection of local anaesthesia rather than general, and general anaesthesia rather than local.

The indications were scored by awarding five points for the first choice made by each consultant, reducing to one point for the fifth. Results have been tabulated in three ways: firstly, the percentage of consultants listing a given indication in their top five choices; secondly, the frequency with which an indication was placed as first choice; thirdly, an 'overall score', calculated as the sum of the scores awarded by all consultants for a given indication and expressed as a percentage. The percentages in the columns 'Consultants placing indicator as first choice' and 'Overall score' do not always total 100 because results have been rounded up or down to the nearest whole number. Results were computer analysed. No regional distinction was made.

Results

Questionnaires were posted to 456 consultants on 4 March 1991. Replies were received from 86% (n=392) by 1 July 1991, at which time the study was concluded. Of these respondents 83%

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Accepted for publication 14 November 1991

Table 1 Method of administration of local anaesthesia

	All consultants (Total 380)	*'Frequent' users of LA* (Total 76)*	*'Infrequent' users of LA (Total 141)*
Retrobulbar	26 (7%)	5 (7%)	13 (9%)
Retrobulbar and facial	178 (47%)	25 (33%)	82 (58%)
Peribulbar	84 (22%)	27 (35%)	17 (12%)
Peribulbar and facial	42 (11%)	6 (8%)	18 (13%)
Facial only	8 (2%)	3 (4%)	1 (1%)
Others	42 (11%)	10 (13%)	10 (7%)

* Local anaesthesia.
Of the 42 (11%) included in the 'other' grouping, 31 (8%) answered two or more options. The remaining 11 (3%) stated a variety of techniques including the 'Redmond Smith' method and 'superior and inferior rectus infiltration with a facial block.'

Table 2 Method of administration of local anaesthesia by specified groups

	'Day case surgery' an indication for LA (Total 213)	*'Speed' an indication for LA (Total 125)*
Retrobulbar	13 (6%)	5 (4%)
Retrobulbar and facial	102 (48%)	57 (46%)
Peribulbar	49 (23%)	33 (26%)
Peribulbar and facial	28 (13%)	15 (12%)
Facial only	4 (2%)	3 (2%)
Others	17 (8%)	12 (10%)

(n=380) had completed the questionnaire in full. Twelve questionnaires were returned uncompleted with explanations attached. Two consultants had retired and replacements had not yet been appointed, one was abroad, and nine no longer carried out cataract surgery as a result of subspecialisation.

The most common technique of cataract extraction was non-automated extracapsular, used by 53% of 380 consultants (n=201) with a further 17% (n=65) performing automated extracapsular surgery. Non-automated endocapsular surgery was preferred by 19% of consultants (n=72), automated endocapsular by 4% (n=15), phacoemulsification by 2% (n=8), and intracapsular surgery by 2% (n=7). The remainder regularly used more than one technique. Intraocular lens implantation was the routine practice of 99% of surgeons (n=376).

The frequency of use of either local or general anaesthesia by each consultant was determined. This allowed analysis of the subgroups 'frequent' users (>75% of cases) and 'infrequent' users (<25% of cases). Local anaesthesia was used 'frequently' by 20% of surgeons (n=76) and 'infrequently' by 37% (n=141).

When performing cataract extraction under local anaesthesia 45% of consultants (n=171) preferred the patient sedated. Oral sedation was prescribed by 26% (n=99) with 11% (n=42) using intravenous, 3% (n=11) using intramuscular, and 5% (n=19) using a combination. Half the 'infrequent' users (n=71) and 42% of the 'frequent' users of local anaesthesia (n=32) routinely sedated the patient. The popularity of intravenous sedation increased among 'frequent' users of local anaesthesia, being employed by 21% (n=16).

Table 3 Indications for selection of local rather than general anaesthesia (total 380 per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score' (see text)*
Medical contraindications	330 (87%)	237 (62%)	1490 (30%)
Day case surgery	213 (56%)	38 (10%)	703 (14%)
Surgeon's preference	168 (44%)	33 (9%)	517 (11%)
Patient's preference	299 (79%)	34 (9%)	1057 (22%)
Cost	90 (24%)	3 (1%)	174 (4%)
Speed	125 (33%)	10 (3%)	298 (6%)
Age of patient	193 (51%)	22 (6%)	583 (12%)
Others	23 (6%)	3 (1%)	70 (1%)

'Others' included 'A necessary evil for waiting lists,' 'Lack of postoperative complications,' 'Administrative pressure' and 'Non-availability of anaesthetist' (most common).

All but one of those surgeons routinely performing intracapsular extraction used local anaesthesia 'infrequently.' There was no other direct association between method of cataract extraction and anaesthetic technique.

The most common method of administration of local anaesthesia was retrobulbar infiltration, used by 54% (n=204) followed by peribulbar, the choice of 33% (n=126) (Table 1). The frequency of use of peribulbar anaesthesia remained similar in the subgroups of surgeons choosing either 'Day case surgery' or 'Speed' as an indication for local anaesthesia (Table 2).

Indications for the selection of local anaesthesia rather than general are presented in Table 3. 'Medical contraindications' was considered the most important indicator, with 'Patient's preference' a close second. 'Day case surgery', 'Age of patient,' and 'Surgeon's preference' achieve similar overall scores. 'Speed' and 'Cost' are the least popular choices. Indications for the selection of local anaesthesia in the subgroups 'frequent' and 'infrequent' users are shown in Tables 4 and 5.

Indications for the selection of general anaesthesia rather than local are presented in Table 6. 'Patient's preference' and 'Stable operating conditions' are the most popular, with 'Ocular conditions' and 'Age of patient' also achieving high 'overall scores.' 'Familiar technique' and 'Anaesthetic opposition' are the least popular of the suggested replies. Indications for the selection of general anaesthesia in the subgroups 'frequent' and 'infrequent' users of general anaesthesia are shown in Tables 7 and 8.

Discussion

In spite of the problems associated with questionnaire based studies the 86% response rate allows a reasonable assessment of current practice to be made. The most common technique in cataract surgery is non-automated extracapsular cataract extraction, which is employed routinely by 53% of consultants (n=201), with 93% (n=353) performing some variant of extracapsular surgery. This contrasts with the 34% regularly performing extracapsular extraction in 1985.[18] Phacoemulsification has been available for many years,[19] but despite the plethora of publicity is practised routinely by only 2% of surgeons (n=8). Several consultants indicated their imminent conversion to this technique. Intracapsular extraction is used routinely by 2% of consultants (n=7), a marked reduction from the 54% of 1985.[18] There has been a dramatic increase in the frequency of intraocular lens implantation, which is now the routine practice of 99% of surgeons (n=376), whereas in 1985 lens implantation was carried out in less than half of all cataract extractions in the UK.[18]

Despite the attention focused on local anaesthesia by lower costs,[5] a shorter post-

Table 4 Indications for local anaesthesia when local anaesthesia used 'frequently' (total 76 consultants per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score'*
Medical contraindications	49 (65%)	26 (34%)	194 (19%)
Day case surgery	44 (59%)	7 (9%)	151 (15%)
Surgeon's preference	51 (68%)	17 (23%)	176 (18%)
Patient's preference	48 (64%)	7 (9%)	164 (16%)
Cost	20 (27%)	1 (1%)	41 (4%)
Speed	37 (49%)	7 (9%)	114 (11%)
Age of patient	42 (56%)	9 (12%)	144 (14%)
Others	10 (13%)	2 (3%)	28 (3%)

Table 5 Indications for local anaesthesia when local anaesthesia used 'infrequently' (total 141 consultants per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score'*
Medical contraindications	132 (94%)	107 (76%)	627 (38%)
Day case surgery	68 (48%)	10 (7%)	243 (15%)
Surgeon's preference	43 (30%)	6 (4%)	133 (8%)
Patient's preference	113 (80%)	13 (9%)	338 (21%)
Cost	37 (26%)	1 (1%)	70 (4%)
Speed	32 (23%)	2 (1%)	67 (4%)
Age of patient	48 (34%)	2 (1%)	135 (8%)
Others	9 (3%)	0	16 (1%)

Table 6 Indications for selection of general rather than local anaesthesia (total 380 per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score'*
Surgeon's preference	203 (53%)	78 (21%)	729 (16%)
Familiar technique	51 (13%)	4 (1%)	125 (3%)
Opposition by anaesthetist	34 (9%)	7 (2%)	99 (2%)
Stable operating conditions	275 (72%)	114 (30%)	1073 (24%)
Patient's preference	295 (77%)	81 (21%)	1140 (25%)
Ocular conditions	209 (55%)	48 (13%)	725 (16%)
Age of patient	181 (48%)	44 (12%)	578 (13%)
Others	29 (8%)	4 (1%)	86 (2%)

Table 7 Indications for general anaesthesia when general anaesthesia used 'infrequently' (total 76 consultants per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score'*
Surgeon's preference	19 (25%)	2 (3%)	51 (6%)
Familiar technique	4 (5%)	0	12 (1%)
Opposition by anaesthetist	7 (9%)	1 (1%)	19 (2%)
Stable operating conditions	45 (60%)	22 (29%)	182 (23%)
Patient's preference	59 (79%)	22 (29%)	239 (30%)
Ocular conditions	38 (50%)	10 (13%)	141 (18%)
Age of patient	38 (50%)	17 (22%)	141 (18%)
Others	3 (4%)	2 (3%)	13 (2%)

Table 8 Indications for general anaesthesia when general anaesthesia used 'frequently' (total 141 consultants per indication)

	Consultants choosing indicator	*Consultants placing indicator as first choice*	*'Overall score'*
Surgeon's preference	104 (74%)	56 (40%)	426 (25%)
Familiar technique	35 (25%)	4 (3%)	95 (6%)
Opposition by anaesthetist	6 (4%)	0	13 (1%)
Stable operating conditions	115 (82%)	50 (35%)	464 (27%)
Patient's preference	97 (69%)	16 (12%)	342 (20%)
Ocular conditions	66 (47%)	9 (6%)	208 (12%)
Age of patient	47 (33%)	6 (4%)	118 (7%)
Others	13 (9%)	0	36 (2%)

operative recovery period,[14] and earlier mobilisation,[16] only 20% of surgeons (n=76) used it 'frequently' (in more than 75% of their cases).

There are several commonly practised methods of administration of local anaesthesia. The traditional technique of retrobulbar infiltration and facial block is the current practice of almost half the consultant population. However, within the subgroup of surgeons using local anaesthesia 'frequently' the popularity of peribulbar anaesthesia increases.

The majority of surgeons (55%, n=209) do not give sedation for cases under local anaesthesia. The preponderance of non-sedators increases to 70% (n=149) among surgeons expressing 'Day case surgery' as their first choice indicator for the selection of local anaesthesia. When sedation is used, it is most frequently oral. Intravenous sedation is given on a regular basis by only 11% of surgeons (n=42). This increases to 21% (n=16) among those using local anaesthesia 'frequently.' Three surgeons are themselves administering intravenous sedation.

Eighty-seven percent of all consultants (n=330) chose 'Medical contraindications' as a reason for selecting local anaesthesia, with 62% (n=236) placing it as first choice. This contradicts the opinion of Rubin[7] that local anaesthesia should be seen as an alternative to general anaesthesia for the more fit and healthy and not as a means of operating on unfit patients. The second most common indication for local anaesthesia is 'Patient's preference,' possibly reflecting at least in part, the growing awareness in the community that this technique is available. 'Cost' and 'Speed' are, interestingly, infrequent first choice indications with correspondingly low 'overall scores'.

In the further analysis of indications for local anaesthesia 'Medical contraindications' appears more important to the 'infrequent' than to the 'frequent' users of local, being chosen by 94% of the former (n=132) and 65% of the latter (n=49), whereas 'Surgeon's preference' is chosen by 68% of the 'frequent' users (n=51) but only 30% of the 'infrequent' users (n=43). 'Speed' is more important to the 'frequent' than to the 'infrequent' users of local anaesthesia, being chosen by 49% (n=37) compared with 23% (n=32). 'Cost' is considered unimportant by both groups equally.

'Day case surgery' as an indication for local anaesthesia was selected by 56% of surgeons (n=213), being the first choice of 10% (n=38). This apparent interest in day case surgery is not reflected in the results of the Cataract Audit Week of the College of Ophthalmologists.[20] Only 8% of the cases performed that week were day cases and many of these were carried out in a small number of 'day case units.'

There has been a marked increase in the use of local anaesthesia compared with 1985.[18] The exclusive use of general anaesthesia was then employed by 63% of surgeons, whereas only 37% (n=141) now use general anaesthesia 'frequently' (in >75% of cases). Six surgeons volunteered the information that they invariably employ general anaesthesia.

Increasing interest in local anaesthesia for cataract surgery has implications for resource management. In addition it has been suggested that a growing number of anaesthetists are themselves interested in administering local anaesthesia for ophthalmic surgical procedures.[7] This has the advantage that the anaesthetist is more involved in the preparation of the patient, but is likely to be resisted by many surgeons, the periocular and orbital tissues traditionally being the domain of the surgeon rather than the anaesthetist.

The most popular indications for the selection of general anaesthesia rather than local are 'Patient's preference,' chosen by 77% of surgeons (n=295) and 'Stable operating conditions,' chosen by 72% (n=275). The importance of 'Stable operating conditions' increases among the 'frequent' users of general anaesthesia, being selected by 82% (n=115) and decreases among the 'infrequent' users, being selected by 60% (n=45). 'Opposition by anaesthetist' was selected as a reason for general anaesthesia by 9% of consultants (n=34). In the further analysis of indications for general anaesthesia 'Surgeon's preference' is a more commonly chosen indicator among the 'frequent' users of general anaesthesia. The same subgroup of surgeons also cites 'Familiar technique' more commonly.

In conclusion, extracapsular cataract extraction is by far the most popular technique in current use with phacoemulsification practised infrequently. Almost all surgeons routinely insert an intraocular lens. There has been a trend towards the use of local anaesthesia, the retrobulbar technique remaining the most popular. Medical contraindications and patient preference are considered the most important indications for selection of local anaesthesia.

We thank the many consultant surgeons whose cooperation in responding so fully and rapidly to our request for information allowed this survey to take place. We are particularly grateful to Professor A R Elkington and Sister M Alexander of Southampton Eye Hospital for their help and guidance.

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British Journal of Ophthalmology, 1992, 76, 327–328

Clinical evidence for the onset of the sensitive period in infancy

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Accepted for publication
5 December 1991

Abstract

Seven neonates had a IIIrd or VIth nerve palsy or afferent visual pathway pathology at birth. These abnormalities resolved within 6 weeks and the children have developed normal visual acuity, motor fusion, and stereopsis. We conclude that there is a latent period of 6 weeks before the onset of the sensitive period.

The neonatal visual system is anatomically, physiologically, and functionally immature at all levels from the eye to the striate cortex and the brain stem and pontine eye movement control centres. For example, most neonates show a constant or intermittent exodeviation[1] and the visual evoked potential is not cortically mediated.[2] The process of maturation whereby normal visual acuity, motor fusion, and stereopsis is achieved takes place over several years. There is behavioural evidence to suggest that sensory stereopsis is established in most infants at 20 to 28 weeks[3] indicating that the receptive fields of binocularly driven striate cortical cells have been established in corresponding positions on the two retinas by that age. However it is not clear at what age after birth the sensitive period for maturation begins.

Neonatal and infantile visual physiology have been extensively investigated experimentally. For example, kittens are born with both eyes closed and under normal circumstances one may open up to 6 days before the other. However, provided both open by day 12 normal binocularity develops. A unilateral lid suture even for a period as short as 7 days after day 12 will result in amblyopia of the occluded eye and absent binocularity, indicating that the sensitive period for the competitive development of cortical binocularity has begun.[4] It is established by such experiments that after the latent period there is a sudden onset of sensitivity to visual deprivation in the cat, a period of high susceptibility, and then a slow decline. The same maturational process is seen in other animals.[5,6] For example, the latent period before the onset of binocular competition and the sensitive period in monkeys is about 21 days.

Table 1 Details of patients

Patient	*Sex*	*Date of birth*	*Lesion*	*Other*	*Time to resolution (weeks)*	*Orthoptic assessment (with age)*
1	M	16.6.86	L VIth	Nil	6	Normal (5 years). Normal Snellen acuity. Stereopsis to 30 seconds
2	M	27.3.90	L VIth	Forceps delivery. Subconjunctival haemorrhage right eye	5	Normal (1 year 6 months). Lang positive
3	F	9.1.90	R VIth	Forceps delivery	4	Normal (1 year 6 months). Lang positive
4	M	9.1.89	R VIth	Nil	4	Normal (2 years 6 months). Vision equal. Lang positive
5	F	14.3.90	R IIIrd	Neonatal meningitis	6	Normal (1 year 6 months)
6	M	2.6.90	L retinal haemorrhages	Exotropia	6	Normal (15 months)
7	M	4.12.90	R lid haematoma	Forceps delivery	5	Normal (10 months)

In man the latent period is less well defined. Experience with unilateral congenital cataracts is conflicting. There is evidence to suggest that good visual results are achieved only with surgery in the first few days of life, indicating a very early onset of sensitivity,[7] although other studies have shown visual acuities of 6/12 or better in those operated on before 17 weeks.[8] None of these children achieved binocularity.

We have studied a group of seven children with either afferent (two cases) or efferent (five cases) abnormalities of the visual system present at birth, but spontaneously resolving over the first few weeks of life. The subsequent development of normal vision and binocularity in these children provides evidence for a latent period of up to 6 weeks before the onset of the sensitive period in infancy.

Patients and methods

The seven children were referred as neonates over a 4-year period and all were examined in the first week of life. (see Table 1). Apart from case 5 who had meningitis, none received any systemic or local treatment. Case 6 had retinal haemorrhages at the posterior pole of the left eye, discovered when the patient was examined because of a constant left exotropia. The eye showed poor fixation but the haemorrhages disappeared by 6 weeks, fixation improved, and the exotropia gradually resolved. All the infants were observed at frequent intervals so that the period before resolution of the abnormality (for example restoration of full eye movement) was accurately measured.

Orthoptic examination consisted of clinical assessment of fixation and visual function with acuity when possible, cover test at near and distance fixation (including 4 dioptre prism fusion test) and assessment of eye movements, motor fusion, and stereopsis. Motor fusion was assessed using base-out prisms of 15 and 20 dioptres. Stereopsis testing was with the Lang test for all children and the Randot test for older patients.

Results

The results are given in Table 1. 'Lang positive' indicates an unequivocally positive behavioural response to the Lang random dot stereotest. In summary, in all seven children the abnormalities present in the first week of life spontaneously resolved by the age of 6 weeks. Subsequently, orthoptic assessment in all these children has been normal.

Discussion

The robustness of the innate capacity for the development of binocularity is illustrated by its frequent normality in infranuclear abnormalities that seriously derange eye movements such as Duane's syndrome or congenital IVth nerve palsy. However in these examples binocular alignment is possible in certain positions of gaze, while before the development of head control, a complete lateral rectus palsy means ocular alignment is never possible. The period of misalignment had no effect on the normal development of binocularity in the four children with lateral rectus palsies that we studied. This indicates that the sensitive period must have started after the recovery of full eye movements at between 4 and 6 weeks of age, otherwise the affected eye would have been amblyopic and cortical binocularity impossible. This finding is consistent with previous reports of neonatal lateral rectus palsy and underlines the benign nature of the condition.[9] By contrast, a post-viral abducens palsy lasting 4 to 6 weeks in an older child is a predictable and potent cause of amblyopia. Similarly, in the girl with neonatal meningitis and a partial IIIrd nerve palsy, the restoration of full eye movements by the age of 6 weeks has been followed by normal visual development. Failure of recovery of normal eye movements in congenital IIIrd nerve palsy always results in profound amblyopia and absent stereopsis even after early surgical treatment. The two children with afferent abnormalities recovered anatomical normality by the age of 6 weeks and developed normal visual acuity in the 'occluded' eye and normal binocularity.

Most of these seven children are not yet old enough for a full assessment of their binocular status to be made. However, considering the seriousness of the pathology at birth, the absence of clinical abnormality suggests a latent period of between 4 and 6 weeks after birth before the onset of the sensitive period.

Defining the latent period is important for several reasons. Firstly, it validates in man the model of the developmental neurophysiology of binocularity resulting from work in experimental animals. Secondly, it is relevant to the aetiology of infantile strabismus. The large angle esotropia characteristic of this condition is not present at birth and is usually noticed from the 6th-8th week onwards, sometimes initially intermittently. Our findings indicate therefore that the onset is within the first few weeks of the sensitive period. The esotropia could be a motor response to a failure of normal competitive afferent visual interaction. Its occurrence when susceptibility to disruption is maximal may explain the failure to develop high grade binocularity even with very early surgical realignment. Thirdly, the onset of the sensitive period is of practical importance in the management of individual cases such as those presented and others, for example, unilateral congenital cataract. The evidence suggests that surgery for a visual result should be timed to achieve optical correction by the age of 6 weeks.

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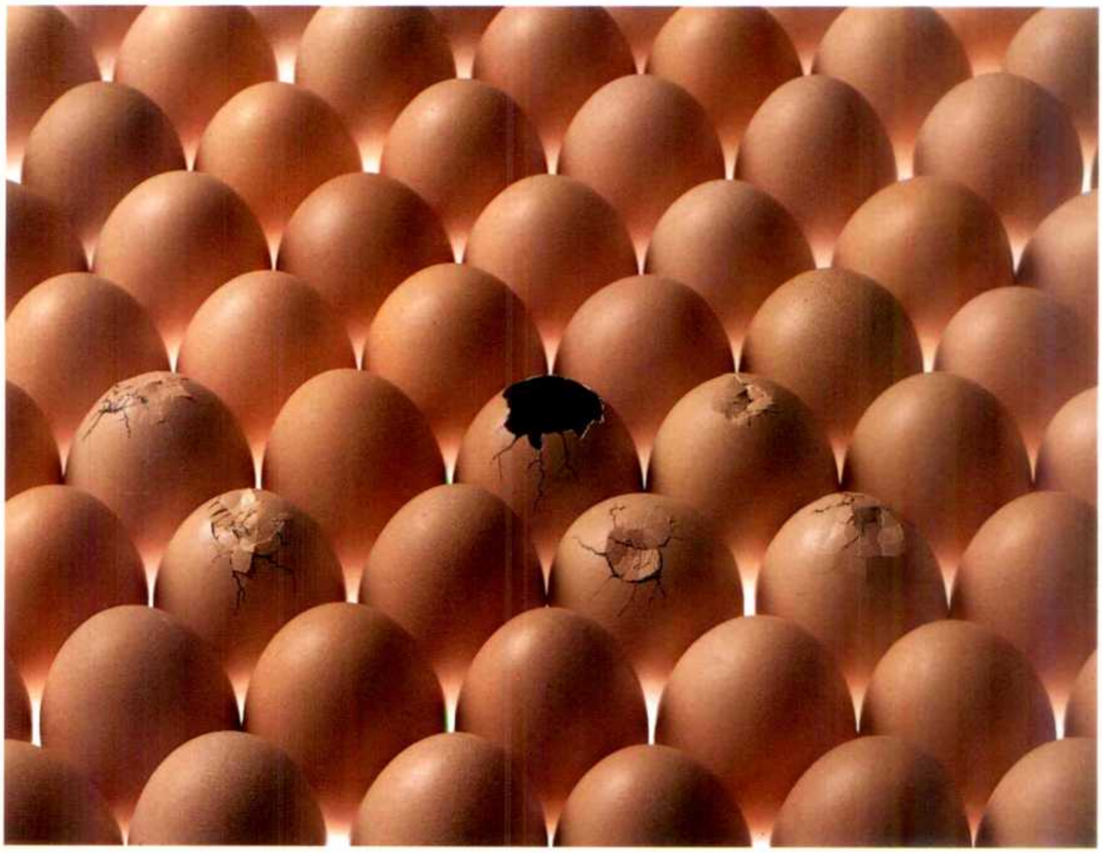
Glaucoma doesn't have to mean the beginning of the end for visual field



Reducing IOP does not necessarily prevent the progression of visual field loss.[1]

Additional factors such as ocular perfusion are now believed to play an important role.[2] It has recently been suggested that maintaining normal ocular vasoregulation whilst lowering IOP can lead to an improved prognosis in glaucoma.[2]

Betoptic, as the only beta$_1$-selective ocular beta-blocker may permit normal vasoregulation as well as effectively lowering IOP.[3,4,5]

In addition, recent clinical evidence suggests that Betoptic is superior to timolol in preserving the visual field.[6]

PRESCRIBING INFORMATION:

PRESENTATION: A clear colourless to light yellow sterile solution containing 0.56% Betaxolol Hydrochloride (equivalent to 0.5% w/v Betaxolol base) and preserved with benzalkonium chloride 0.01% w/v. **USES:** BETOPTIC is indicated for the reduction of elevated intra-ocular pressure in patients with ocular hypertension and chronic open-angle glaucoma. **DOSAGE AND ADMINISTRATION:** The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS AND PRECAUTIONS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic has demonstrated a low potential for systemic effects, it should be used with caution in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. Although cardioselective beta-blockers have less effect on lung function than non-selective beta-blockers caution should be exercised in the treatment of glaucoma patients with obstructive pulmonary disease. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon installation and occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have been reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depressive neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies have not demonstrated any specific hazard there are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response this drug should be used during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known whether Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is administered to nursing mothers. **TREATMENT OF OVERDOSE:** A topical overdose of Betoptic may be flushed from the eye(s) with warm tap water. **BASIC NHS PRICE:** £5.30 per 5ml Droptainer. **PRODUCT LICENCE HOLDER AND NUMBER:** Alcon Laboratories (UK) Ltd, PL 0649/0097. Further information is available on request from Alcon Laboratories (UK) Ltd, Imperial Way, Watford, Herts WD2 4YR. Telephone (0923) 246133. Betoptic is a trademark of Alcon Laboratories.

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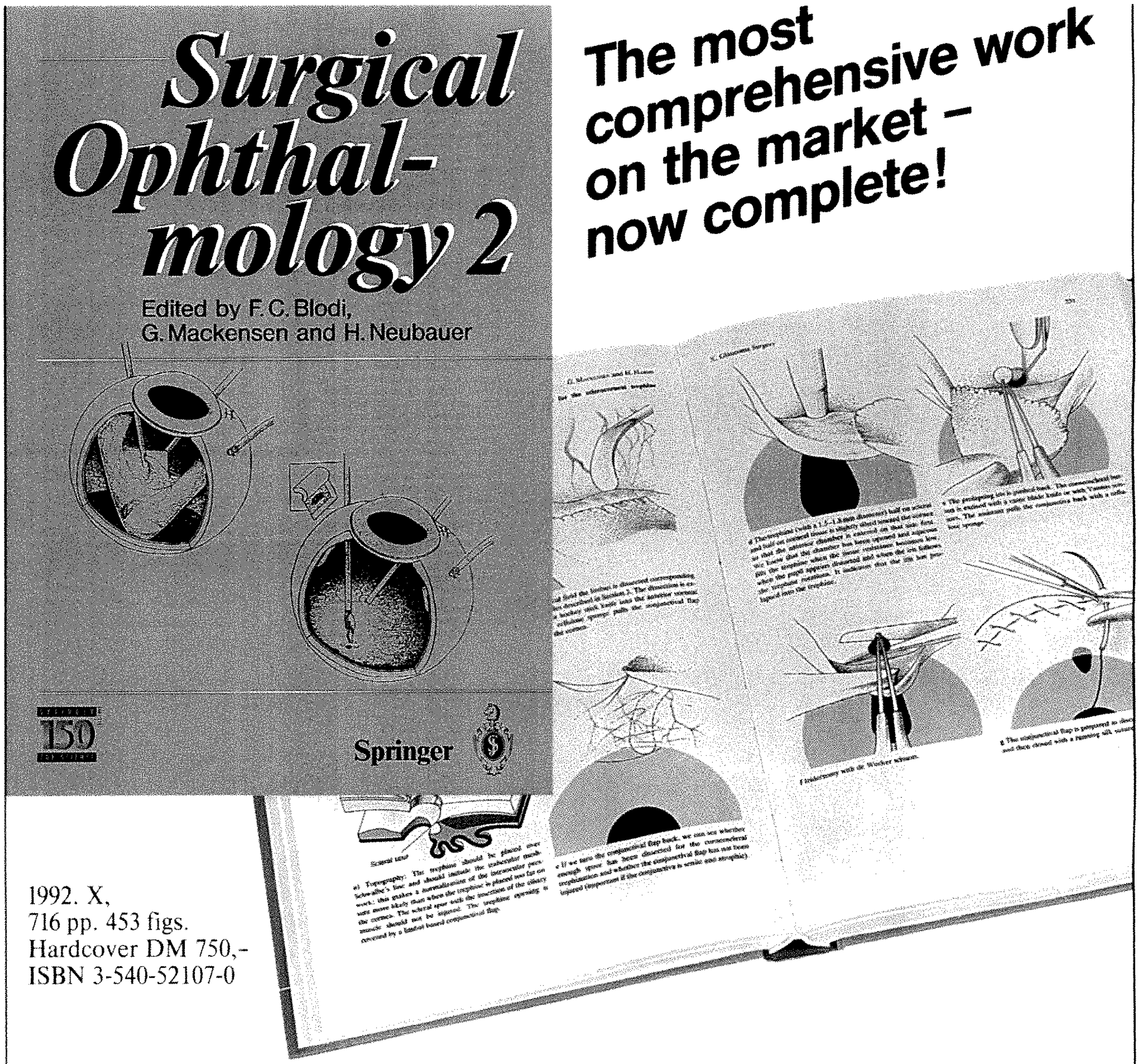

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British Journal of Ophthalmology, 1992, 76, 329–331

Sequential argon-YAG laser iridotomies in dark irides

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Accepted for publication 29 November 1991

Abstract

Laser iridotomies in dark coloured irides are associated with higher complication and failure rates. A prospective clinical study to evaluate the use of the argon and Nd:YAG laser in sequential combination for iridotomy was carried out on 20 eyes of 13 patients with dark irides. Patent iridotomies were achieved in single treatment sessions for all the eyes. Iridotomy closure was observed in one eye during a mean follow-up period of 14 months (range 6–20 months). Complications from the treatment occurred in five eyes and were minor. Total mean energy used for the argon and Nd:YAG stages respectively were a third of most studies on pure argon and Nd:YAG iridotomies. Sequential argon-YAG laser iridotomy combines most of the advantages of both laser types while avoiding some of their disadvantages. We find it a safe and effective tool for iridotomy in otherwise difficult dark irides.

Laser iridotomy is now a well established procedure for the management of angle closure glaucoma and for prophylaxis in fellow eyes. Many ophthalmologists consider the Nd:YAG laser the ideal iridotomy tool especially for blue irides. However the YAG laser does not work as effectively in thick dark brown irides. The higher complication and failure rates in these patients whether by argon or YAG laser are well recognised and documented.[1-4]

Schwartz[1] using a pulsed argon laser reported 20% failure to penetrate in brown eyes. Quigley[2] reported needing two or more sessions to achieve patent argon iridotomies in 58% of his patients with dark brown irides. Tomey[3] stated that the higher amount of YAG laser energy required by his patients was attributed to the high prevalence of thick, brown irides among his patients.

Some authors[4,5] have documented the secondary use of the Nd:YAG laser at separate treatment sessions to salvage an otherwise failed argon iridotomy. We conducted this study to evaluate a method of iridotomy using the argon and Nd:YAG laser in sequential combination at the same sitting to penetrate the iris.

Table 1 Patient characteristics

Patient no	*No of eyes*	*Diagnosis*	*Iris colour*	*Race*
1	2	CAC/FE	DB	Ch
2	2	AAC/FE	DB	Ch
3	2	AAC/FE	DB	Ch
4	1	AAC	DB	Ch
5	1	FE	DB	Ind
6	1	FE	DB	Ch
7	1	FE	DB	Ch
8	2	CAC/CAC	DB	Ch
9	2	CAC/CAC	DB	Ch
10	2	CAC/CAC	DB	Ch
11	1	CAC	DB	Ind
12	2	CAC/CAC	DB	Ch
13	1	FE	DB	Ch

CAC=chronic angle closure; FE=fellow eye; Ch=Chinese; AAC=acute angle closure; DB=dark brown, Ind=Indian.

Materials and methods

Twenty eyes of 13 patients were treated. All eyes had dark brown irides and were treated by the same investigator. There were 11 Chinese and two Indian patients. Ten eyes had creeping angle closure glaucoma, three had acute angle closure, and seven were contralateral eyes (Table 1). The mean period of follow-up was 14 months (range 6–20 months). The average age of the patient was 62 years (range 45–82).

We used the Coherent Medical 920 Argon laser with a Zeiss slit-lamp delivery system for the first stage and the Cooper Vision 2300 Q-Switched Neodymium YAG laser for the second perforation stage.

Prior to the laser therapy all patients had a complete ophthalmic examination. Eyes with very shallow anterior chambers, iritis, or corneal oedema were excluded. Informed consent was obtained and topical pilocarpine 2% four times daily was administered the day before the procedure. After administration of topical anaesthesia an Abraham lens was inserted. Whenever possible an iris crypt in the mid-periphery was selected as the iridotomy site. The argon laser was used as the first stage laser. Initial argon laser parameters were standardised at (1) spot size 50 μm, (2) power 700 mW, and (3) duration 0·1 second. We found it important to pre-empt the formation of a black pigment crust as this will absorb the incident laser energy without vaporising and effectively forms a barrier to further penetration. Should charring occur the duration and/or power may need to be shortened and/or reduced. Good penetration was characterised by vapour bubble formation with minimal iris charring. It was not advisable to shoot through a large vapour bubble as accurate focus and visualisation cannot be ascertained. Large vapour bubbles at the iridotomy site can be displaced easily by tapping the Abraham lens with a finger. On the other hand, we found that small vapour bubbles serve as a condensing lens and shooting through these was safe and resulted in good penetrating shots. The inital bore was made to an estimated depth of about two thirds iris thickness with an approximate diameter of 300 to 500 μm.

The Nd:YAG laser was used as the second stage laser to achieve iris perforation. Energy levels were set between 2 and 5 mJ depending on the surgeon's estimate of the depth of penetration achieved at the end of the first stage. All shots were delivered in single pulse mode.

All patients had their IOP measured at 1 hour postoperatively. Patients with an IOP rise not greater than 10 mm Hg above preoperative levels were given prophylactic Diamox (acetazolamide) 250 mg twice daily for the next 2 days. If the IOP rise was greater than 10 mm Hg at 1 hour postoperatively the patient was given an immediate dose of 500 mg acetazolamide and monitored for up to 3 hours as it is well documented that most IOP rises occur within the first 3 hours postoperatively.[6-8] Topical steroids were given for 1 week to all patients after the procedure.

Results

We were able to achieve patent iridotomies in all 20 eyes at the same sitting. For the first argon laser stage the mean number of shots needed to achieve the initial bore was 55 (SD 26, range 15–140; Tables 2 and 3). The mean power used was 810 mW (SD 181, range 600–1100; Tables 2 and 3). It was often necessary to vary the duration of the shots during the procedure to achieve penetration and to avoid charring the iris. The duration of the argon laser shots ranged from 0·01 second to 0·1 second (Table 2). For the second perforation stage, which was done using the Nd:YAG laser, the mean number of shots needed was 4 (SD 2, range 1–6; Tables 2 and 3). Energy settings usually started off at 2 mJ depending on the surgeon's estimate of the depth of iris penetration achieved at the end of the first stage. The mean energy setting was 4 mJ (SD 1·2, range 2–5).

The mean total energy delivered per eye by the argon and Nd:YAG lasers respectively were 3·6 J and 9·4 mJ.

Table 2 Sequential argon-YAG iridotomy – laser parameters

Patient no	*Glaucoma type*	*No of argon shots*	*Average power (mW)*	*Average duration (seconds)*	*No of YAG shots*	*Energy setting (mJ)*
1	CAC	50	900	0·05	2	2
	FE	50	1100	0·05	1	2·4
2	AAC	50	700	0·03	4	3
	FE	50	600	0·02	1	2·4
3	AAC	34	1100	0·1	4	4
	FE	38	1100	0·1	2	4
4	AAC	50	700	0·1	2	5
5	FE	50	700	0·1	3	2·5
					1	3
6	FE	40	700	0·1	3	2·5
7	FE	15	1000	0·1	6	2·4
					3	2
8	CAC	82	1000	0·01	3	2·5
	CAC	140	700	0·01	1	4
					2	2
9	AAC	70	700	0·1	2	5
	CAC	70	700	0·1	1	5
10	CAC	45	600	0·1	1	5
	CAC	50	700	0·1	1	5
11	CAC	18	1100	0·1	2	3
12	CAC	50	700	0·1	2	5
	CAC	80	600	0·1	3	3
13	FE	62	800	0·1	3	5

Table 3 Mean laser parameters

1st stage	*Mean argon parameters (SD)*	
Power (mW)	810 (181)	(range 600–1100)
Exposure (seconds)	0·08 (0·03)	(range 0·01–0·1)
No of shots	55·0 (26·0)	(range 15–140)
Mean total energy delivered per eye (J)	3·6	
2nd stage	*Mean ND:YAG laser parameters (SD)*	
Energy setting (per shot, mJ)	4·0 (1·2)	
No of shots (single mode)	4·0 (2·0)	(range 1–9)
Mean total energy delivered per eye (mJ)	9·4	

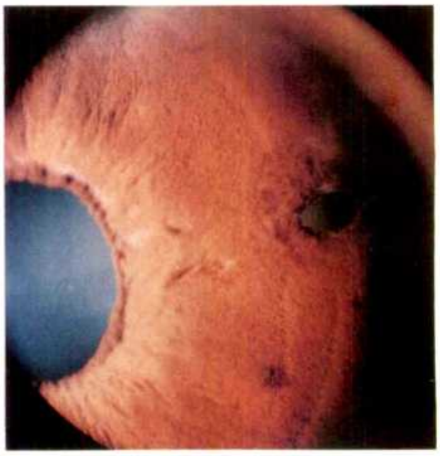

Figure 1 Typical sequential argon-YAG iridotomy. Large, round iridotomy with sharp margins.

Microhyphaema was seen in two eyes. Focal lens opacity was noted in one eye. Focal corneal endothelial opacity was seen in two eyes. Immediately following the iridotomy all the eyes had various degrees of pigment dispersion and free floating debris. However no clinically significant inflammation was present by the end of the first week. Five of the eyes had intraocular pressure rises over 10 mm Hg within the first hour. However they responded well to acetazolamide treatment. Iridotomy closure was observed in one eye during a mean follow-up period of 14 months (range 6–20 months).

Discussion

Certain features of the argon laser makes it an effective iridotomy tool in dark coloured irides. (1) The incident laser energy is well absorbed and penetration can therefore be achieved at relatively low thermal settings, (2) hyphaema, which is a common occurrence with YAG iridotomies is uncommon, and (3) pigment dispersion is minimal compared with YAG iridotomies.

However the high energy absorption often causes significant charred pigment crust formation which acts as a barrier to further penetration. This, together with the thicker iris,

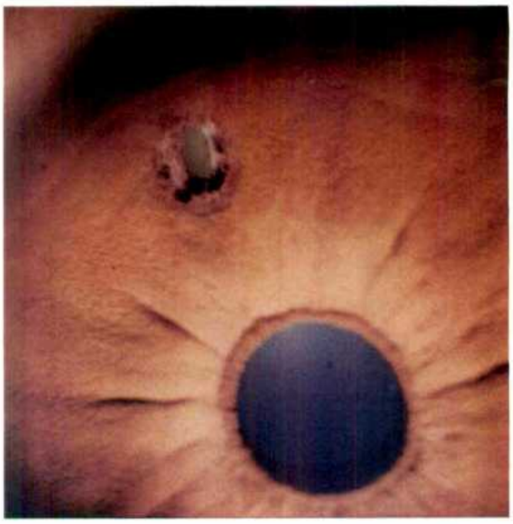

Figure 2 Another example of iridotomy achieved with this method.

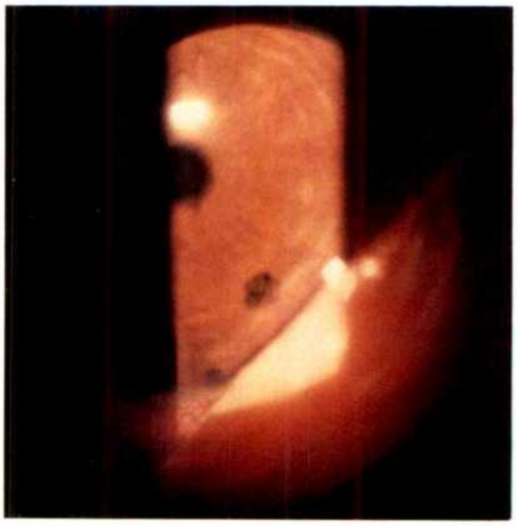

Figure 3 Patient at end of first argon laser stage.

means more shots are often needed to create a patent iridotomy. Indeed Ritch[9] has reported using 300 to 400 shots with argon laser settings at 1 W power, 0·02 second duration, and 50 μm spot size in patients with dark brown irides. This is of concern as central endothelial cell loss due to the indirect thermal effects of the laser has been documented.[6] In our study we found the mean total energy delivered per eye by the argon and YAG respectively is only a third of the corresponding values reported for pure argon and YAG iridotomies.[6-8] This should have a significant bearing on complications resulting from either direct or indirect thermal damage to the eye.

The iridotomies created were typically large, round, and with sharp margins (Figs 1 and 2). This is in contrast to the slit opening of YAG iridotomy and the argon iridotomy where the hole is smaller with charred edges.

Complications resulting from the treatment were minor. Microhyphaema was seen in two eyes (10%). This is in contrast to pure YAG iridotomies where about 40% are complicated by bleeding.[6-8] This advantage is probably conferred by the use of the argon laser as the first stage laser.

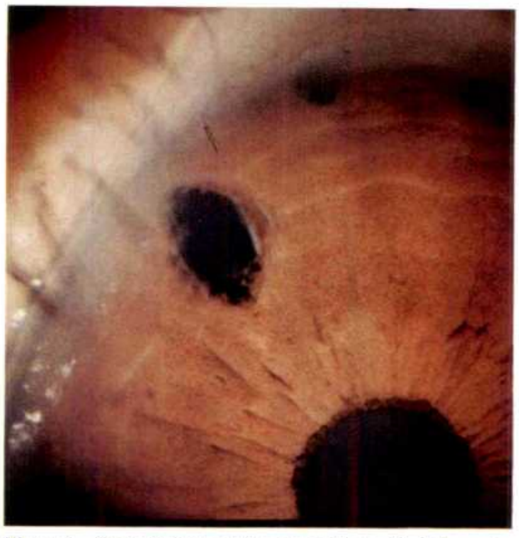

Figure 4 Same patient as Figure 3 at 10 months follow-up. In this patient the iridotomy demonstrated spontaneous enlargement to twice its original size.

One of the major advantages of YAG iridotomy is that it is rarely associated with focal lens damage. This is because the zone of optical breakdown and plasma formation following YAG laser shots extends not distally but proximally towards the laser source, a phenomenon termed the 'plasma shield effect'. On the other hand the incidence of focal lens damage in argon iridotomy has been reported to be between 35 and 53%.[6-8] Our study showed a low incidence possibly due to the use of the YAG laser as the second stage laser.

Focal corneal endothelial opacity was seen in two eyes (10%) and this rate is similar to that reported by most studies on pure argon and YAG iridotomies.[6-8]

Closure rates of 21–31% have been reported in pure argon laser iridotomy whereas it is well established that YAG laser iridotomy appears to show no tendency to close in eyes uncomplicated by rubeosis or iritis although the exact mechanism remains unclear.[7,8] Iridotomy closure was noted in only one eye during a mean follow-up period of 14 months (range 6–20 months). Could the use of the YAG as the second stage laser be the reason for these low closure rates?

An interesting phenomenon of spontaneous progressive iridotomy enlargement was observed in some eyes. In one particular patient the iridotomy enlarged to almost twice the original iridotomy size over a 10 month follow-up period (Figs 3 and 4). It is our clinical impression that this phenomenon occurred in about a third of the eyes, albeit to a much lesser degree.

We observed two further advantages from this procedure. (1) Macula injury from inadvertent argon laser shots is very unlikely with this method and therefore one is not restricted to using only the nasal side for the iridotomy site. (2) The hazardous and time consuming chipping and enlargement phase necessary in argon iridotomy is not necessary.

Conclusion

This study suggests that sequential argon-YAG iridotomy is a safe and effective procedure and combines the advantages of both laser procedures while avoiding most of their disadvantages. It could well be the ideal iridotomy tool for dark coloured irides.

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British Journal of Ophthalmology, 1992, **76**, 332–335

Dapsone therapy for the acute inflammatory phase of ocular pemphigoid

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Accepted for publication 1 August 1991

Abstract

Oral dapsone was used to treat five patients who presented in the acute inflammatory phase of ocular pemphigoid. The diagnosis was made clinically by identifying cicatricial changes which were in some cases difficult to find. In all cases it was the inflammatory rather than the cicatricial features which responded to treatment. An initial dose of 100 mg/day was effective without toxicity. When 150 mg/day was used patients experienced side effects. A clinical response was obtained after 1–4 weeks and could be maintained on a dose of between 50 mg on alternate days and 100 mg/day. Therapy was withdrawn during remissions which lasted up to 32 weeks but all cases required continuing therapy which has remained effective. Immunopathological examination was carried out on two occasions in all cases and although positive on at least one occasion the results did not correlate with disease activity or treatment. The inflammatory phase of ocular pemphigoid should be added to the list of diseases responsive to dapsone.

Cicatricial pemphigoid is a disease of unknown aetiology which results in chronic progressive blistering and scarring of mucosal epithelium. The oral mucosa is most commonly affected with the conjunctiva involved in 75% of cases and the skin in 21–30%.[1 2 3] The eye changes are characterised by subepithelial fibrosis with symblepharon formation. There is also an acute inflammatory form of the disease with redness and swelling of the conjunctiva.[4] In these cases of florid inflammation the cicatricial changes may be overlooked and the condition misdiagnosed.

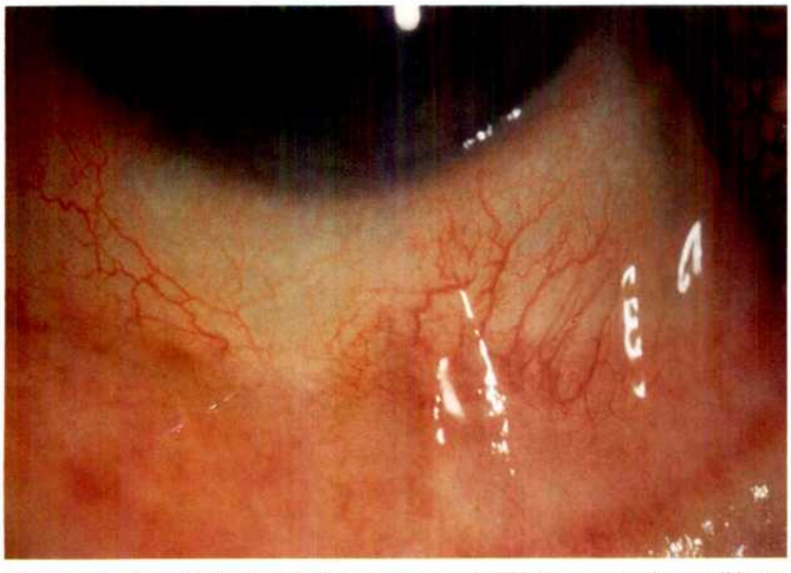

Figure 1 Early symblepharon in the lower fornix (case 4). This feature was often so mild as to be overlooked on initial examination.

Dapsone and other drugs of the sulfone group have been used for many years, particularly in dermatological practice to treat a variety of inflammatory conditions. Katz[5] lists 13 dapsone responsive conditions including dermatitis herpetiformis. Dermatological reports have suggested the drug may have an effect on a proportion of patients with cicatricial and bullous pemphigoid[6 7 8] but there is little information about its effect on ocular disease. We describe the value of dapsone in the treatment of the acute inflammatory features of ocular pemphigoid.

Patients and methods

We studied five consecutive patients between 1984–1990 who had ocular cicatricial pemphigoid in the acute inflammatory phase. None had a history of other causes of cicatricial conjunctivitis such as chronic infection, chemical trauma, or Stevens-Johnson syndrome.

Whether or not there was a history of skin lesions all patients were examined by a dermatologist.

The first two patients were commenced on dapsone 150 mg/day but both developed haemolysis and one became cyanosed. Subsequent patients were therefore given a starting dose of 100 mg/day in divided doses and the dose was reduced to the minimum required to maintain a clinical response. Where possible treatment was discontinued but if the condition relapsed the drug was re-introduced at the previous maintenance dose.

While taking the drug each patient's blood was examined regularly for evidence of haemolysis or anaemia.

Conjunctival and skin biopsies and serum samples for immunological assay were taken from each patient while they were without treatment and the disease was active and when the condition was in remission during treatment. Conjunctival biopsies were taken by a snip of upper bulbar conjunctiva elevated with forceps under topical anaesthesia with amethocaine 1% eye drops. Skin snip biopsy was taken from normal skin on the volar surface of the forearm after subcutaneous injection of 1% lignocaine with adrenaline. The specimens were frozen in liquid nitrogen and direct immunofluorescence staining performed with fluorescein-labelled antisera to human IgG, IgA, IgM, and C_3. Indirect studies were performed for circulating antibodies to conjunctival epithelium and its basement membrane zone.

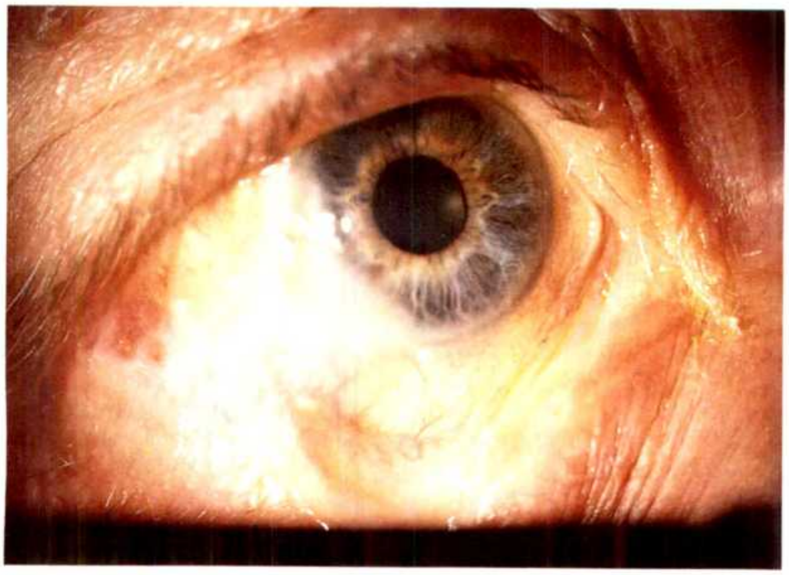

Figure 2 Advanced symblepharon with corneal pannus and scarring identified at presentation (case 2).

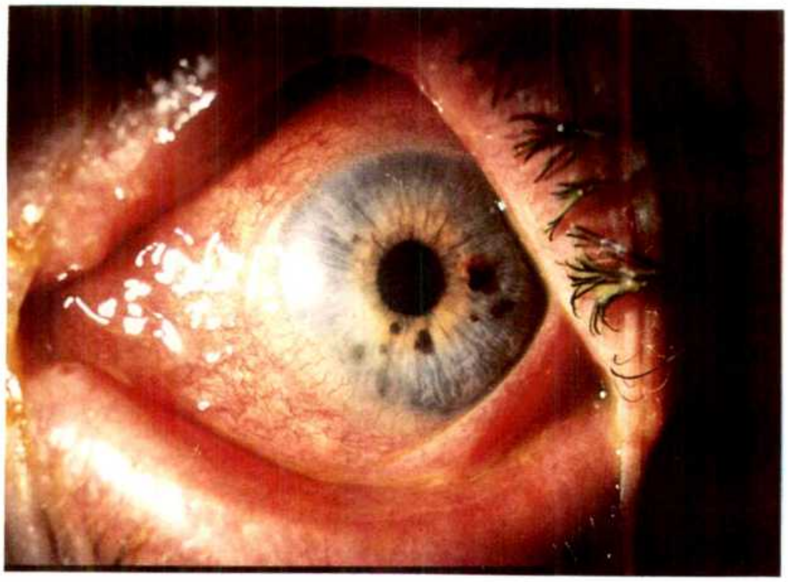

Figure 3 Inflamed conjunctiva prior to treatment (case 4).

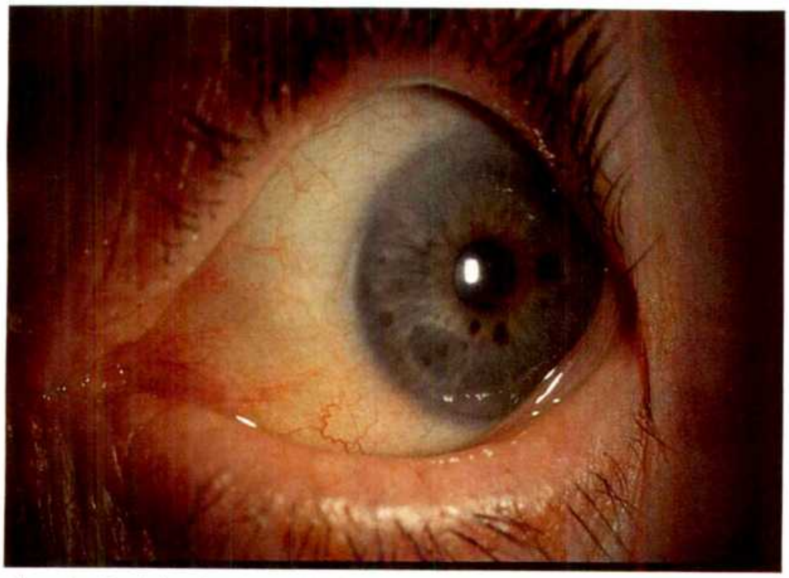

Figure 4 Remission of conjunctival inflammation 1 month after starting dapsone therapy. Same patient as Figure 3 (case 4).

Results

The mean age of the three male and two female patients was 60 years (range 40–72 years). Three of the five cases presented with undiagnosed chronic conjunctivitis resistant to treatment. The diagnosis was eventually made clinically when previously overlooked subconjunctival fibrosis and symblepharon were identified (Fig 1). Selective involvement of the medial or lateral canthus was not present. In the other two patients cicatricial changes were obvious on presentation (Fig 2) allowing more rapid diagnosis.

Though there was cicatrisation in all cases the main presenting problem was chronic conjunctival inflammation with discomfort and pain. Figure 3 shows the inflammed conjunctiva of one patient and Figure 4 the same eye in remission on therapy. While both eyes were involved in every case there was often marked asymmetry. On stopping the drug the latent period before recurrence of the disease varied between patients and for individual patients on different occasions ranging from 1 week to 8 months.

Patient 1 had required treatment for 20 years for primary open angle glaucoma; formerly with topical adrenaline and pilocarpine latterly topical metipiranolol and oral dichlorphenamide. Topical glaucoma therapy was stopped when pemphigoid was diagnosed but the dichlorphenamide was continued.

The acute inflammatory element of ocular pemphigoid responded to the drug in all cases with a clinical response noted between 1–4 weeks after starting dapsone (Table 1). The response time varied for different patients but was consistent for each patient on every occasion the drug was recommenced. Some patients had initially received antibiotic and steroid drops but these were discontinued when the inflammation first responded to dapsone and could not account for the improvement in the patients' conjunctival appearance. Although the conjunctival inflammation was controlled by dapsone one case needed supplementary systemic steroid when severe corneal and scleral involvement occurred.

Toxic reactions to dapsone occurred at doses of 100 mg/day or more. There was one case of mild jaundice and one of cyanosis and haemolysis. Both patients were able to continue effective long term therapy at reduced dose.

Dermatological examination identified only one patient with a skin disorder and this was described as psoriaform dermatitis after skin biopsy and is inconsistent with cicatricial pemphigoid. Two patients had oral signs suggestive of pemphigoid.

The immunofluorescent assay results are shown in Table 2 and categorised according to whether the patient was taking dapsone or not. Conjunctival biopsy did not stimulate ocular inflammation or progression of conjunctival fibrosis. No consistent pattern of immunological results can be detected.

Discussion

The cicatricial features of ocular pemphigoid are well recognised but the acute manifestations of the disease are not. Mondino[1] reports swollen

Table 1 Patient details and response to dapsone showing minimum maintenance dose and length of asymptomatic remissions without treatment. All patients still require therapy

Patient	*Age (yrs)*	*sex*	*Response time (weeks)*	*Maintenance dose of dapsone*	*Duration of remission off dapsone (weeks)*
1	67	F	2	50 mg/day	6–32
2	63	M	2–4	50 mg/day	4
3	43	M	2	100 mg/day	10–16
4	72	F	3	50 mg/alternate days	1–16
5	59	M	1	50 mg/day	1

mounds of conjunctiva during episodes of acute disease activity which interrupt and exacerbate the conjunctival shrinkage. Wright[9] includes conjunctival ulceration with fluorescein staining in the clinical diagnostic criteria for ocular cicatricial pemphigoid. The patients reported in our paper illustrate the acute inflammatory features of conjunctival induration and vascular dilatation with chronic ocular irritation. It is these aspects that responded to dapsone therapy.

Although the condition is rare[10] the diagnosis of ocular pemphigoid should be considered in any patient presenting with undiagnosed conjunctival inflammation. There is a condition with cicatricial conjunctivitis known as linear IgA disease which is responsive to dapsone.[11] None of our patients had any extraocular lesions consistent with linear IgA disease or dermatitis herpetiformis.

Case 1 may represent pseudo-pemphigoid initiated by 20 years of topical antiglaucoma therapy.[12 13 14] However the persistence of acute conjunctival inflammation after discontinuing topical medication makes the diagnosis less likely. The association of pemphigoid and topical therapy for glaucoma has been described by Tauber *et al*[15] who found that 26% of 111 cases of ocular cicatricial pemphigoid had a history of medical therapy for glaucoma for an average of 11 years. Nearly all had this treatment before the onset of pemphigoid suggesting that glaucoma medication may be a causative factor. Whether this is a separate 'pseudo-pemphigoid' condition or merely pemphigoid in which the usually idiopathic trigger factor has been identified it is known they are histologically and immunologically indistinguishable.[16 17] Both seem to respond equally to dapsone.

Cicatricial pemphigoid remains a clinical diagnosis. Immunological tests may confirm the diagnosis when positive but do not exclude the diagnosis when negative. Only two patients in our study showed the diagnostic finding of linear immunoglobulin deposition at the conjunctival basement membrane (cases 2 and 4) and this disappeared when the patients were taking dapsone. One other (case 3) had circulating IgG and IgA to conjunctival basement membrane but paradoxically the serum immunoglobulins were only present when the patient was taking dapsone and disappeared when treatment was discontinued. Several patients had antibodies to conjunctival epithelium on direct and indirect testing but this has been shown to be a non-specific finding in several chronic conjunctival conditions.[18 19] Immunological findings in pemphigoid are known to be inconsistent[20] and do not correlate with extent or activity of disease.[21]

Table 2 Summary of immunofluorescent results. Tests were carried out both on and off treatment in every case. Although positive on at least one occasion in each case the pattern did not correlate with either disease activity or treatment

	On dapsone				*Off dapsone*			
Patient	*Clinical state*	*Conj*	*Skin*	*Serum*	*Clinical state*	*Conj*	*Skin*	*Serum*
1	Inactive	ND	−ve	IgA (C)	Inactive	ND	ND	IgA (C)
2	Inactive	ND	ND	−ve	Active	IgA (L)	−ve	−ve
3	Inactive	IgA (E)	−ve	IgG (BM) and IgA (BM)	Inactive	−ve	−ve	−ve
4	Inactive	−ve	−ve	−ve	Inactive	IgA (L)	−ve	−ve
5	Inactive	IgA (E)	−ve	−ve	Active	−ve	−ve	IgG (C)

L=linear; E=intraepithelial; C=to conjunctiva; BM=to basement membrane; ND=not done.

From our study it seems that an initial dose of 100 mg/day should be effective with little risk of side effects. A maintenance dose of between 50 mg/day and 50 mg on alternate days seems adequate. In practice once control was achieved patients were able to adjust their own maintenance dose. This varied with the severity of their symptoms and at all times they remained under medical supervision. Rogers *et al*[7] recommend an initial low dose and a gradual increase over a 2 week period to the therapeutic level but they found the ocular features of pemphigoid less responsive to dapsone than mucosal ulceration elsewhere. We observed remissions of variable duration but all patients eventually relapsed and the fact that the relapsed patients were repeatedly brought into remission again within 2 weeks of recommencing the drug was the most convincing clinical evidence that dapsone is effective in this condition. Side effects have been reported with dapsone principally haemolysis and methaemoglobinaemia. Doses of more than 50 mg/day invariably produce a degree of haemolysis which seldom lowers the haemoglobin level by more than 1 g but does elevate serum bilirubin. Unless patients have cardiopulmonary problems or pre-existing anaemia the drop in haemoglobin is usually well tolerated. Methaemoglobinaemia is not a major problem and even in patients taking 200 mg of dapsone per day the level does not usually exceed 12% of the total haemoglobin and is often less than 5%.[5] This may give the patient a grey cyanosed appearance but is otherwise asymptomatic. Dapsone is relatively non-toxic and particularly in an elderly population seems safer to use than other possible means of treatment such as systemic steroids or immunosuppressants.[22 23]

The mode of action of dapsone is unknown despite considerable investigation. The drug appears to act by inhibiting the migration of neutrophilic polymorphonuclear leucocytes. Whether this is achieved by inhibiting lysosomal enzyme activity,[24] interfering with the leucocytes' cytotoxic system[25] or preventing the cell responding to chemotactic stimuli[26] remains to be established.

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FIFTY YEARS AGO

Syphilis

War brings many horrors in its train; not the least of these is an increase in syphilis.

I indicated at the outset that syphilis had shown a definite annual decline in the years preceding the present war. I regret that the number of new acute cases is now beginning to show an alarming increase; this will not be seen in ophthalmology until later on, but unless the acute cases are properly treated it will surely occur, it may be not for ten or fifteen years, when the congenital syphilitic children reach puberty or the half treated cases arrive with lesions of the central nervous system.

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British Journal of Ophthalmology, 1992, 76, 336–337

Diffractive multifocal intraocular lens implants for unilateral cataracts in prepresbyopic patients

Peter J Gray, M G Lyall

Abstract

Multifocal intraocular lenses allow pseudophakic patients to obtain good near and distance visual acuities without an additional near correction. We report our experiences in implanting diffractive multifocal intraocular lenses in prepresbyopic patients with acquired unilateral cataracts and assess their postoperative visual acuities and stereoscopic vision. Accommodative function in patients following cataract surgery is discussed.

Extracapsular cataract extraction with the insertion of a posterior chamber intraocular lens is a safe and effective means of treating cataracts which provides an almost identical optical system to that of the human eye. But the pseudophakic eye is unable to accommodate because the intraocular lens is of a fixed power, and this necessitates a separate near addition. Clear vision for both distance and close work can, however, be offered to patients by inserting an intraocular lens with multifocal optics. These utilise the 'simultaneous vision principle' whereby separate images of near and distant objects are formed and, if the power difference between the two optical systems is at least 3.00 dioptres, the images are dissimilar enough for the brain to interpret them as separate, select the highly focused one relating to the object of regard, and suppress the other. This can be achieved with two distinct optical elements (the refractive or bull's eye type of multifocal intraocular lens) or by means of diffractive optics,[1] where concentric diffractive zones are applied to the posterior surface of the implant in order to focus light from near objects.

We report our experiences in implanting a diffractive multifocal intraocular lens (3M Vision Care) in prepresbyopic patients with acquired cataracts that have developed after the critical period for visual development.

Patients and methods

We report on a consecutive series of five prepresbyopic patients with acquired unilateral cataracts who received a diffractive multifocal intraocular implant between August 1989 and March 1990. Their clinical histories are detailed in Table 1. The patients, and parents if appropriate, were advised of the risks and benefits of the procedure, to which they accordingly gave informed consent. Preoperative biometry was performed in order to calculate the intraocular implant power. All of the cataract extractions were performed by a single experienced surgeon (ML) under general anaesthesia using a standardised endocapsular technique. All of the operations were uncomplicated. Postoperatively the patients were reviewed until their pseudophakic vision had stabilised, at which time they were assessed with regard to unaided visual acuity in each eye for far, near, and intermediate objects (by reading a Snellen chart or reading test type at 10, 15, 30, and 50 cm and 1 and 6 m); the amplitude of clear vision (depth of focus) was measured for an N8 target; and the stereoscopic visual acuity was determined by means of the TNO or Titmus stereotests.

Results

The patient's stereoscopic visual acuity was classified into four grades: – grade 1 (less than 40 seconds of arc); grade 2 (40 to less than 60 seconds of arc); grade 3 (60 to 100 seconds of arc); and grade 4 (over 100 seconds of arc). These results and the patient's visual acuities with targets at various distances for both the pseudophakic eye and the normal accommodating eye are listed in Table 1. It should be noted that all these results are unaided, except for patient C, a myope, who used a contact lens and whose planned pseudophakic myopia was also corrected with a contact lens. The follow-up period varied from 12 to 18 months (mean 14 months).

In addition bilateral multifocal intraocular lenses were implanted asynchronously in a 27-year-old woman with both Huntington's chorea and diabetes mellitus who developed acute diabetic cataracts. She unfortunately died 4 months after surgery but was able to spend her final weeks with clear distance vision (6/9) and clear near vision (N8) without the need for spectacles or contact lenses which would have been difficult in view of her neurological condition.

Discussion

Harold Ridley inserted the first intraocular lens with the intention of correcting the anisometropia of unilateral aphakia in order to restore binocular vision.[2] He realised that the pseudophakic eye was unable to accommodate, though the phenomenon of 'pseudoaccommodation', which is often between 2·00 and 4·00 dioptres, does occur, but only in a small number of cases. Thus the possibility of achieving Ridley's aim for the perfect restoration of binocular vision with the intraocular implant fulfilling all the physiological functions of the human lens has only recently been fully achieved with the introduction of multifocal intraocular lenses which can permit

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Accepted for publication
31 October 1991

Table 1 Summary of results

Patient	*A**		*B**		*C†*		*D*		*E*	
Age at surgery	*6 years*		*16 years*		*22 years*		*25 years*		*25 years*	
Eye	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
Ocular status	*Normal*	*Steroid-induced cataract*	*Perforating injury*	*Normal*	*Perforating injury*	*Normal*	*Perforating injury*	*Normal*	*Normal*	*Perforating injury*
Preoperative visual acuity	6/6	3/60	<6/24	6/4	CF	6/6 (+CL)	CF	6/5	4/4	CF
Postoperative unaided acuities:										
Snellen at 6 m	6/6	6/9	6/5	6/4	6/6 (+CL)	6/6 (+CL)	6/9	6/5	6/5	6/9
Near vision test type at 1 m	N12	N24	N14	N8	N14 (+CL)	N10 (+CL)	N14	N10	N10	N12
Near vision test type at 50 cm	N10	N12	N10	N6	N10 (+CL)	N9 (+CL)	N10	N8	N9	N10
Near vision test type at 30 cm	N8	N8	N6	N5 (+CL)	N9 (+CL)	N8 (+CL)	N8	N6	N6	N8
Near vision test type at 15 cm	N6	N8	N5	N4·5	N6 (+CL)	N4·5 (+CL)	N6	N4·5	N5	N6
Near vision test type at 10 cm	N10	N10	N12	N10	N12 (+CL)	N6 (+CL)	N10	N12	N10	N12
Depth of focus for an N8 target (cm)	12–40	14–32	13–38	15–55	14–24	8–34	12–32	14–54	12–45	10–33
Grade of stereoscopic vision	2		1		3		4		3	

* Developed a posterior capsule opacity which required a Nd-YAG capsulotomy.
† All measurements were with a contact lens myopic correction.

binocular functioning for both close and distant vision without any additional spectacle correction.

The inability of the eye to accommodate after cataract surgery is of little handicap to the elderly patient who has been habituated to using a reading correction. However, this 'acquired presbyopia' will cause greater inconvenience to young patients accustomed to the process of accommodation. This will be more marked in unilateral cases, where there is little or no depth of focus in the pseudophakic eye yet normal accommodation in the dynamic fellow eye. These patients will have binocular vision for distance, yet be able to see clearly monocularly only for near. They are ideal candidates for multifocal intraocular lenses and become accustomed to the clear near vision of these implants more quickly than elderly patients (personal observations), whose brains have already 'forgotten' about intrinsic accommodative mechanisms and have been conditioned to use reading glasses for near vision.

Previous reports on multifocal intraocular lenses have compared the functioning of the multifocal intraocular lens with that of a monofocal intraocular lens in the fellow eye. This is the first study on multifocal intraocular lens function in younger patients with active accommodation in a phakic fellow eye. The reported series is small because, while it is comparatively easy to collect many patients with senile cataracts, cataracts in younger patients are much less common, and hence no statistical inferences can be made. However, all the patients obtained two peaks of clear vision, one at infinity (achieving at least 6/9) and the other between 15 and 30 cm, where they could read N8 or smaller, and most had stereoscopic vision. The diffractive multifocal implant therefore allowed these patients to correct all the optical problems of unilateral aphakia without the need for any spectacle correction. No patient specifically complained of any postoperative visual disturbance such as haloes, which have been described in some patients who have received multifocal intraocular lenses.[3]

Thus the diffractive multifocal intraocular lens has considerably improved the quality of life of all persons who received it. There has been much discussion[3] of the relative merits of implanting multifocal intraocular lenses, but the patients concerned have been elderly, with bilateral cataracts, and accustomed to using a reading correction prior to surgery. But this report concerns the advantages conferred by such lenses on prepresbyopic patients, who often have unilateral cataracts with normal accommodation in the fellow eye. Here the multifocal intraocular lens allows the pseudophakic eye to function in an integrated fashion with its fellow eye which has active accommodation.

We gratefully acknowledge the assistance given in the orthoptic assessment of these patients by Miss Jones and Miss Owen-Flood.

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British Journal of Ophthalmology, 1992, 76, 338-341

Synthesis of interleukin-1 and prostaglandin E$_2$ by lens epithelial cells of human cataracts*

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Abstract

To test our hypothesis that pseudophakic inflammation, including the fibrin reaction, may be caused by cytokines, prostaglandins (PG), or both, synthesised by residual lens epithelial cells (LECs), we measured interleukin-1α (IL-1α) and PGE$_2$ in the incubation medium of cultures of human LECs obtained by capsulotomy during cataract surgery. After 1 week radioimmunoassay showed that there were 1·46 (0·62) ng of PGE$_2$/10^6 cells (mean (SD) six cultures), and after 4 weeks, there were 5·50 (2·20) ng of PGE$_2$/10^6 cells (seven cultures). During culture the cells proliferated and underwent fibroblast-like cell changes on exposure to the plastic of the wells. In the medium of control plates to which sodium diclofenac had been added PGE$_2$ was not detected. Some IL-1α was found in four of 10 samples, each of which contained media from 12 cultures; 207 pg/10^6 cells in one of the two pools of 2-week cultures, 120 pg/10^6 cells in one pool and 139 pg/10^6 cells in another of the three pools of 3-week cultures, and 111 pg/10^6 cells in the one pool of 4-week cultures. PGE$_2$ and IL-1α may therefore be produced in vivo by residual LECs after cataract surgery, and may be involved in postoperative inflammation, including the fibrin reaction.

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Accepted for publication
15 November 1991

In our previous clinical study[1] we showed that residual lens epithelial cell (LECs) participated in postoperative inflammation including fibrin reaction[2-5] after intraocular lens implantation.

Aqueous flare intensity (measured by a laser flare cell meter[6]) decreasing from an initial peak owing mainly to surgical trauma, increased again to form a second flare peak, when residual LECs came into contact with the posterior chamber lens and began to undergo fibrous proliferation at 6 to 14 days after surgery. The spike was evidence that the blood-aqueous barrier had been disrupted again. In the eyes, in which residual LECs had been removed by ultrasound aspiration, neither such a flare spike nor fibrous proliferation of residual LECs was noted.

We postulated that residual LECs synthesise prostaglandin E$_2$ (PGE$_2$) and cytokines such as interleukin-1 and transforming growth factor, during their fibrous proliferation, and these mediators are responsible for the renewed breakdown of the blood-aqueous barrier.

To test this hypothesis we measured PGE$_2$ and interleukin-1α (IL-1α) in the incubation media of cultured human LECs, and the results are reported here.

Materials and methods

TISSUE CULTURE OF HUMAN LECS

Circular pieces of the anterior capsule with LECs attached obtained by capsulotomy during cataract surgery were cultured directly without the cells being dispersed. To prevent contamination of the anterior capsules with blood cells the corneoscleral incision was thoroughly cauterised with more than usual care, and after circular capsulorhexis the piece of capsule was touched with an irrigation/aspiration tip and withdrawn from the eye by aspiration. While being held with fine forceps the piece of capsule was thoroughly washed with irrigating solution. Then each piece of anterior capsule was placed immediately into a well of a 48-multiwell plate containing 0·5 ml of Eagle's minimum essential medium containing 10% fetal calf serum, penicillin G at 100 U/ml, and streptomycin sulphate at 100 mg/l. The pieces were observed carefully under an inverted phase-contrast microscope to check for contamination with blood cells, and cultured in 100% humidity at 37°C with a 5% CO$_2$ atmosphere. The medium was changed every 7 days.

Cell growth in each culture was observed daily under the phase-contrast microscope.

EXPLANTS AND SAMPLE COLLECTION

For the PGE$_2$ experiment 24 explants from patients with senile immature cataracts were divided into two groups. Cells from 13 explants not treated with sodium diclofenac were cultured as described above; six specimens for 1 week and seven for 4 weeks. Cells from 11 other explants were cultured in the same way except that 10 mg/l sodium diclofenac, a non-steroidal anti-inflammatory drug, was added to each culture. If the medium was changed, sodium diclofenac was added again at the same concentration. Six of the treated specimens were cultured for 1 week and five for 4 weeks. Samples of the culture medium were collected as described below.

For the IL-1α experiment 120 specimens were cultured for 1 to 6 weeks and samples of media were collected. Culture was not continued after the collection. Each sample consisted of media pooled from 12 cultures. Two samples were collected after 1 week of culture, two samples after 2 weeks, three samples after 3 weeks, and one sample after 4, 5, and 6 weeks. At these times the culture medium was sampled with a small pipette and frozen immediately at −20°C. In both experiments the cells remaining in each well were counted as described below.

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* Part of this paper was presented at the 13th Biannual Meeting of the International Ophthalmic Microsurgical Study Group (IOMSG), 4-8 September, 1990, in La Baule and at the 8th European Intraocular Implant Council (EIIC), 10-14 September, 1990, Dublin.

CELL COUNTS

Each well was washed with 0·5 ml of phosphate-buffered saline free from calcium and magnesium, and the cells were then incubated again in the same wells in 0·4 ml of a mixture of 0·25% trypsin and 0·02% EDTA 2Na for 10 min at 37°C. After repeated pipetting to remove cells from the capsule and the plastic of the well, the entire cell suspension was transferred into a small glass test tube, with care to leave as few cells as possible in the well. The cells were stained by the addition of 0·1 ml of a mixture of 0·05% crystal violet and 2·1% citric acid, and then the addition of one drop of formalin. Only viable cells were stained. The viable cells in three samples of medium were counted in a Fuchs-Rosenthal's cell chamber for the counting of erythrocytes.

MEASUREMENT OF PGE_2 AND IL-1α IN THE INCUBATION MEDIUM

PGE_2

The PGE_2 concentration in the culture medium was measured with an RIA kit containing ^{125}I-labelled PGE_2 (New England Nuclear Corp, Boston, MA, USA). We used the assay procedure in the kit manual modified as reported elsewhere.[7,8] In brief, 0·5 ml of culture medium at 4°C was acidified with 0·05 M citrate at pH 3·5. C-18 extraction cartridge columns ((Bond-Elut) 200 mg, Analytichem International, Inc, Harbor City, CA, USA) were first treated with 2 ml of methanol and 4 ml of 0·05 M citrate. The acidified medium was then passed through the cartridge and eluted with 2 ml of distilled water, 2 ml of 10% methanol, 2 ml of cyclohexane, and 2 ml of ethyl acetate, in that order. The last solvent was evaporated at 37°C under a stream of nitrogen.

The minimum detectable amount of PGE_2 by this method was 0·25 pg/tube. Results are given an nanograms of PGE_2 per 10^6 cells.

IL-1α

The culture medium of each sample was concentrated 10 times in a Centricon-10 apparatus (WR Grace and Co, Beverly, MA, USA), so that substances with molecular weights of 10 000 or less were removed. The filtrate was centrifuged at 3000 rpm for 6 hours. The IL-1α concentration in the supernatant was assayed with an IL-1α ELISA kit (Otsuka Pharmaceutical Co, Tokushima, Japan). The minimum detectable amount was 10 ng/l. Results are given as picograms of IL-1 per 10^6 cells.

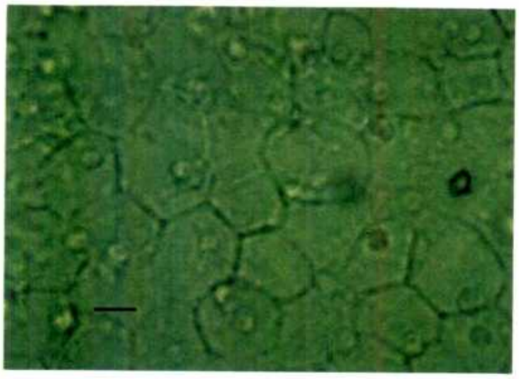

Figure 1 Uncultured human lens epithelial cells observed under an inverted phase-contrast microscope. The cells are mostly hexagonal, and the nuclei and cell boundaries are distinct. (Bar, 12·5 μm.)

Results

HUMAN LEC CULTURE

In the first preparations a few blood cells were found in some cultures, which were discarded. The red blood cells could be easily differentiated from LECs, which are polygonal and were mostly attached to the lens capsule. After we took more care with preventing contamination it was no longer detected.

The anterior capsule usually curled upward with the side to which the LECs were attached facing downward, so that the LECs in the centre of the capsule came into direct contact with the well. Where the capsule touched the well, LECs began to proliferate within 2 or 3 days. All proliferating cells lost their initial polygonal shape (Fig 1) and underwent pleomorphic changes, becoming slightly elongated and fibroblastic (Fig 2). As the attached cells underwent these changes and while the areas of attachment were expanding, the anterior capsule became

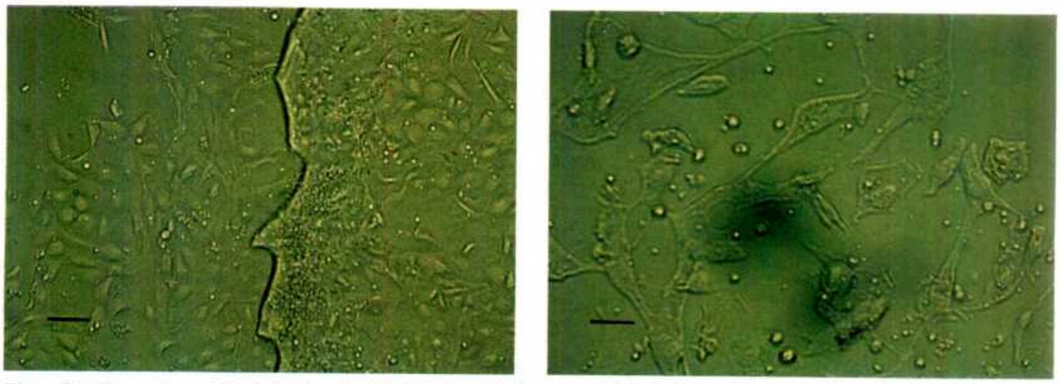

Figure 2 Human lens epithelial cells cultured for 7 days. Left: Lens epithelial cells, which are touching the dish, have started to show pleomorphic changes, and are proliferating in the direction opposite from the capsule on the right. (Bar, 125 μm.) Right: Cells in the area beyond the capsule are elongated and fibroblastic in appearance. (Bar, 50 μm.) The PGE_2 concentration was 2·34 ng/10^6 cells.

fixed to the well and the curled edge gradually flattened. With the pleomorphic changes, the cell boundaries and nuclei became indistinct under the phase-contrast microscope (Fig 2).

From about 1 week after culture began untreated cultured specimens showed cells proliferating to confluence on the capsule, and growth beyond the capsular margin (Fig 2). After 4 weeks the cells were still proliferating and had become almost confluent. In some cultures LEC proliferation was confined to the capsule. Four of the six specimens cultured for 1 week and treated with sodium diclofenac for the PGE_2 measurements were restricted to moderate cell growth compared with the untreated specimens. Of specimens cultured for 4 weeks, treated cultures had fewer cells than untreated cultures (Tables 1A and 1B).

MEASUREMENT OF PGE_2

PGE_2 was detected in the medium from all the untreated cultures. The mean PGE_2 concentration for untreated specimens cultured for 1 week was significantly higher ($p<0·01$, Student's *t* test) than that for untreated cells cultured for 4 weeks (Table 1). However, PGE_2 was detected in only two media from the six treated specimens cultured for 1 week, and the concentration was low, though the cells had slow to moderate growth.

Table 1A PGE_2 concentration in culture medium of human lens epithelial cells

	Untreated		*Treated*	
Specimen no	*Cell numbers*	*PGE_2 (ng/10^6 cells)*	*Cell numbers*	*PGE_2 (ng/10^6 cells)*
1	$1·7\times10^4$	0·68	$0·7\times10^4$	0·0
2	$2·5\times10^4$	0·88	$1·5\times10^4$	0·0
3	$2·4\times10^4$	2·34	$0·8\times10^4$	0·18
4	$2·6\times10^4$	1·33	$0·8\times10^4$	0·24
5	$1·9\times10^4$	1·83	$1·4\times10^4$	0·0
6	$2·5\times10^4$	1·71	$0·1\times10^4$	0·0
		1·46 (SD 0·62)		0·07 (SD 0·11)

Culture was for 1 week.

Table 1B PGE_2 concentration in culture medium of human lens epithelial cells

	Untreated		*Treated*	
Specimen no	*Cell numbers*	*PGE_2 (ng/10^6 cells)*	*Cell numbers*	*PGE_2 (ng/10^6 cells)*
1	$3·5\times10^4$	2·4	$0·7\times10^4$	0·0
2	$2·2\times10^4$	4·76	$0·2\times10^4$	0·0
3	$2·4\times10^4$	4·27	$0·3\times10^4$	0·0
4	$3·5\times10^4$	7·95	$0·2\times10^4$	0·0
5	$3·6\times10^4$	4·72	$1·5\times10^4$	0·0
6	$3·5\times10^4$	8·21		
7	$3·7\times10^4$	6·59		
		5·50 (SD 2·20; $p<0·01$)		0·0

Culture was for 4 weeks.

Table 2 Interleukin-1 concentration in human lens epithelial cell culture media

Culture duration (week)	*Cell no ($\times10^5$)*	*IL-1α (pg/10^6 cells)*
1	0·65	ND
	0·40	ND
2	0·79	ND
	0·86	207
3	0·83	120
	1·03	139
	1·16	ND
4	1·05	111
5	0·91	ND
6	0·85	ND

ND = not detected.

MEASUREMENT OF IL-1α

IL-1α was detected in one of the two samples of specimens cultured for 2 weeks, in two of three samples cultured for 3 weeks, and in the one sample cultured for 4 weeks (Table 2). In the control media without LECs, IL-1α was not detected.

Discussion

PGE_2 is synthesised by various ocular tissues[9-13] and is important in intraocular inflammation because it disrupts the blood aqueous barrier. There are only a few reports on the possible contribution of the crystalline lens to PG biosynthesis,[14-19] and the lenses of some species have been found not to produce PGs.[14 15]

Taylor *et al*[16] did not detect PGs in the medium of cultured calf LECs by RIA. However, Belisle *et al*[17] presented evidence suggesting that rat LECs synthesise PGs. Keeting *et al*[18] reported on PGE_2 synthesis by homogenised rat lenses. Fleisher and McGahan[19 20] reported on PGE_2 synthesis by lenses from experimentally inflamed rabbit eyes. There are no published reports of PG synthesis by human LECs.

Here we found that PGE_2 was synthesised by epithelial cells of human crystalline lens from patients with cataracts. PGE_2 was detected in every untreated medium.

Sodium diclofenac was used at the concentration of 10 mg/l because this dose suppresses the biosynthesis of PGE_2 without being very toxic. The number of cells was small in the treated cultures, but viable cells remained. In some cultures sodium diclofenac suppressed cell growth only slightly, but PGE_2 was not detected in these cultures either. Therefore 10 mg/l diclofenac could be used in the controls.

To set in motion the arachidonic acid cascade, which leads to PGE_2 synthesis, some stimulation is needed.[21]

Tissue injury during surgery and cell culture preparation could affect the PGE_2 concentration in the culture medium. However, as we found increased PGE_2 concentrations in older cultures after 4 weeks, such injury is unlikely to have stimulated the cells to continue to produce the increasing amount of PGE_2 detected.

Another factor that might affect the amount of PGE_2 synthesised is changes in tissue and cell morphology during culture; that is, the proliferation of cells and the growth of fibroblast-like cells. Human LECs undergo fibroblast-like cell changes (fibrous metaplasia) on exposure to the dish plastic in tissue culture.[22-24] Such morphological changes do not resemble the normal state of the lens in an intact lens capsule, but reflect a response to stimulation or to pathological conditions.

Our results therefore suggest that exposure of human LECs to the plastic of the well stimulated PGE_2 synthesis in tissue culture. Further, in untreated cultures, the PGE_2 concentration at 4 weeks was significantly greater than that at 1 week, so the rate of synthesis of PGE_2 by LECs was greater at 4 weeks than at 1 week. We postulate that it increases as LEC proliferation, with fibroblast-like cell change, advances.

The cytokine IL-1 is one of the peptide mediators involved in both the up and down regulation of immunological, inflammatory, and reparative host responses to injury; the cytokines act at concentrations of 10^{-10} to 10^{-15} mol/L.[25,26] Because these small quantities impede the purification, and the minimum detectable amount for IL-1 was 10 ng/l, we pooled the incubation media of 12 cultures and concentrated the pool obtained 10 times to make one sample.

IL-1 was detected in four untreated samples after 2, 3, or 4 weeks. That IL-1α was not detected in the six other samples does not prove that IL-1α was not synthesised in those cultures. It may not have reached a detectable level in the earlier cultures.

IL-1 is produced by monocytes, macrophages, lymphocytes, epithelial cells, endothelial cells, fibroblasts, and synovial cells.[26] There have been no reports of IL-1 synthesis by LECs of any species, including humans.

Most normal cells that can produce IL-1 will do so only when stimulated by one of a variety of agents.[26] Here, as in PGE_2 synthesis, contact between the LECs and the well plastic may have been a stimulant to IL-1 synthesis.

IL-1α increases PGE_2 synthesis[25] by activating phospholipase,[27] lipoxygenase,[28] and cyclogenase[29] in the arachidonic acid cascade. We therefore think that IL-1 was first produced on exposure to the well plastic, and it stimulated the LECs to synthesise PGE_2.

The tissue culture that we used, with human LECs attached to the anterior capsule cultured directly without cell dispersion, resembles the in vivo condition after cataract surgery. After cataract surgery residual LECs proliferate, showing fibrous metaplasia in the defective, avascular lens capsular bag containing an intraocular plastic lens. This condition is analogous to the tissue culture model used, in which LECs attached to the torn anterior capsule proliferate and show fibroblast-like cell change on exposure to the plastic of the wells.

Moreover, our report[1] that the blood-aqueous barrier was disrupted again at 6 to 14 days postoperatively while residual LECs underwent fibrous proliferation at the defective capsular margin after intraocular lens implantation is consistent with the present results.

That PGE_2 and IL-1α are detected in the culture media suggests that, in vivo also, residual LECs may synthesise these compounds.

In conclusion, IL-1α and PGE_2 were detected in culture media of human LECs and could be produced also in vivo by residual LECs after cataract surgery. They may have an important role in the pathogenesis of postoperative inflammation, in aphakic and pseudophakic eyes.

We thank Drs M Imayasu and A Mizumoto of Menicon Co, Ltd, Nagoya, Japan, for the cell counts.

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British Journal of Ophthalmology, 1992, **76**, 342–345

Outcome of strabismus surgery in congenital esotropia

J M Keenan, H E Willshaw

Abstract

The results of squint surgery in 40 children with congenital esotropia are analysed. A 'favourable outcome' was achieved in 23 (57·5%) children. The factors affecting the final outcome including ocular alignment in the immediate postoperative period, age at the time of surgery, amblyopia, associated inferior oblique overaction, dissociated vertical deviation, latent or manifest latent nystagmus, and the surgical procedures used are discussed.

Congenital esotropia is an esodeviation with an onset before 6 months of age,[1] characterised by a large stable angle, a limited potential for binocular single vision, and an association with oblique muscle dysfunction, dissociated vertical deviation (DVD), and latent or manifest latent nystagmus.[2] The results of surgery in congenital esotropia have been classified by von Noorden[2] into (1) orthotropia or asymptomatic heterophoria with subnormal binocular vision, (2) microtropia, (3) small angle (<20 dioptres) and cosmetically acceptable residual esotropia or consecutive exotropia, and (4) large angle (>20 dioptres) residual esotropia or consecutive exotropia that requires additional surgery. However others have categorised as cosmetically acceptable only those aligned within 10 dioptres of straight and furthermore alignment within 10 dioptres of straight prior to 24 months of age may significantly improve the prospects of developing binocular single vision.[3]

The initial surgical procedures used to attain alignment include monocular recession–resection,[4] bimedial rectus recessions,[5] and three and four horizontal muscle surgery,[6] any of which may be combined with conjunctival recessions[7] and/or inferior oblique muscle surgery.[8]

We reviewed children under our care who underwent surgery for congenital esotropia, and who had a follow-up of at least 2 years, to determine the results achieved, to identify the factors associated with satisfactory and less satisfactory outcomes, and to consider this information in the planning of future surgery for this condition.

Patients and methods

The case notes of consecutive patients undergoing surgery for congenital esotropia at the Children's Hospital, Birmingham, in the 5 year period between January 1982 and December 1986 were reviewed. Congenital esotropia was defined as the onset of esotropia in the first 6 months of life, with no significant accommodative component.[9] Any patient with a neurological deficit or ocular pathology and all those with a follow-up of less than 24 months were excluded. Information was obtained from the preoperative examination and from examinations at 2 weeks, at 3–6 months, and at yearly intervals thereafter until discharge.

Amblyopia was defined as a difference of two lines or more between the monocular visual acuities using appropriate correction where necessary. Anisometropia was defined as a spherical or cylindrical difference of more than 1·0 dioptre between the two eyes.[10] All refractions were undertaken under cycloplegia using either cyclopentolate or atropine.

Statistical analysis was performed using medians and the non-parametric Mann-Whitney test for comparing continuous variables, and the χ^2 test with Yates' correction or Fisher's exact test for categorial data.

Results

The inclusion criteria were met by 40 patients. There was an equal male/female sex distribution. The age at surgery ranged from 8 to 71 months (median 21 months), the preoperative squint angle from +25 to +60 dioptres (median +50 dioptres), and the postoperative follow-up from 24 to 83 months (median 44·5 months). The surgery undertaken is detailed in Table 1.

The final alignment obtained for the whole group is detailed in Table 2. A single operation was performed for 26 children (65%), and a second procedure was carried out for the remaining 14 (35%). A residual esotropia of more than 20 dioptres was present in four patients; two were considered cosmetically acceptable and two were scheduled for further squint surgery.

There was evidence of binocular single vision postoperatively in 11 patients (27·5%); nine showed motor fusion and two gross stereopsis demonstrable with the synoptophore. The final

Table 1 Surgical procedures with numbers of cases (and percentages) undertaken for congenital esotropia

Bimedial rectus recessions	15 (37·5%)
Bimedial rectus recessions with conjunctival recessions and bilateral inferior oblique myectomies	7 (17·5%)
Bimedial rectus recessions with conjunctival recessions	6 (15·0%)
Bimedial rectus recessions with bilateral inferior oblique myectomies	5 (12·5%)
Monocular medial rectus recession/lateral rectus resection	4 (10·0%)
Bimedial rectus recessions with faden sutures	1 (2·5%)
Bimedial rectus recessions with faden sutures and conjunctival recessions	1 (2·5%)
Monocular medial rectus recession with faden suture and conjunctival recession/lateral rectus resection	1 (2·5%)

Table 2 Final alignment obtained in 40 children with congenital esotropia

Within ±10 dioptres of straight	20 (50%)
Between ±10 dioptres and ±20 dioptres	16 (40%)
More than +20 dioptres	4 (10%)

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Accepted for publication
17 October 1991

Table 3 Postoperative squint angles in the favourable and less favourable outcome groups at 3–6 months postoperatively (p=0·042)

Postoperative squint angle	*Favourable outcome*	*Less favourable outcome*	*Row total*
Within ±15 dioptres of straight	19	8	27
More than ±15 dioptres	4	9	13
Column total	23	17	40

alignment was within ±10 dioptres of straight in eight of these patients; two had a consecutive exotropia of 14 dioptres and one a residual esotropia of 20 dioptres. A final alignment within ±10 dioptres of straight was also present in 12 patients who showed no evidence of binocular single vision postoperatively.

A 'favourable outcome' was considered to be present in 23 (57·5%) children. There was evidence of binocular single vision in 11 (the final alignment was within ±10 dioptres of straight in eight of these patients; two had a consecutive exotropia of 14 dioptres and one a residual esotropia of 20 dioptres); and the remaining 12 patients had a final alignment within ±10 dioptres of straight with no evidence of binocular single vision.

POSTOPERATIVE ALIGNMENT

When the 23 patients with a favourable outcome were compared with the 17 patients with a less favourable outcome, no significant difference was found between the median age at onset of squint (1 month vs at birth), median age at surgery (19 vs 27 months), median preoperative squint angle (+50 dioptres in both groups), incidence of amblyopia at the time of surgery (21·7 vs 23·5%), incidence of anisometropia (26·1 vs 17·6%), or incidence of further surgery (30·4 vs 41·2%). The only difference between the two groups was in the postoperative squint angle measurement at 3–6 months, with significantly more of the favourable outcome group achieving alignment within ±15 dioptres of straight at that time (Table 3).

Ocular alignment at the first postoperative visit was not found to be a reliable predictor of favourable outcome. Furthermore, in 10 patients the strabismus angle changed by more than 10 dioptres between the first and second postoperative examinations; seven children with residual esotropia showed a reduction in their esotropia, one child with residual esotropia increased, and the only two children with an immediate consecutive exotropia showed an increase in their divergent angle.

EARLY SURGERY

Squint surgery was performed in 23 patients before their second birthday, with 16 (69·6%) of these children achieving a favourable outcome, compared to a favourable outcome in seven of 17 children (41·2%) whose surgery was performed after their second birthday.

Alignment within ±15 dioptres of straight at the 3–6 month postoperative examination was present in 11 of the early surgery group prior to their second birthday, and nine of these 11 patients (81·8%) achieved a favourable outcome.

Alignment within ±15 dioptres of straight at the 3–6 months postoperative examination was present in a further 16 patients after their second birthday (eight of these patients were in the early surgery group but were not aligned until after their second birthday), and a favourable outcome was achieved in 10 of these 16 patients (62·5%). These results did not achieve statistical significance.

AMBLYOPIA

Amblyopia treatment was required in 26 patients (65%) prior to surgery, nine of whom remained amblyopic at the time of surgery. In the group of 17 patients who had their amblyopia successfully reversed prior to surgery a favourable outcome was present in nine (52·9%). In the nine patients who remained amblyopic at the time of surgery a favourable outcome was present in only three (33·3%).

Nine patients not amblyopic at the time of surgery required postoperative amblyopia treatment; six of these had received preoperative amblyopia treatment, but in three there was no history of preoperative amblyopia. Despite requiring postoperative amblyopia treatment six of these nine patients (66·6%) still achieved a favourable outcome.

Anisometropia was present in eight patients preoperatively, six of whom required amblyopia treatment. Three remained amblyopic at the time of surgery; one had a hypermetropic cylindrical anisometropia and two a combined hypermetropic spherical and cylindrical anisometropia. Postoperatively a favourable outcome was achieved in five of the nine patients (55·6%).

INFERIOR OBLIQUE OVERACTION, DVD, LATENT OR MANIFEST LATENT NYSTAGMUS

Inferior oblique overaction was present in 12 patients (30%) preoperatively, all of whom had bilateral inferior oblique myectomies combined with horizontal squint surgery. A further four patients (10%) developed inferior oblique overaction after their initial surgery. A favourable outcome was obtained in nine of these 16 patients (56·3%); the remainder had a residual esotropia of greater than 10 dioptres.

Dissociated vertical deviation occurred in six patients (15%), all with onset after their initial surgery. Surgical correction was required in one. A favourable outcome was obtained in five of these patients.

Latent nystagmus (LN) was present in four patients, and one had manifest latent nystagmus (MLN). A favourable outcome was achieved in four of these patients, including the child with MLN.

SURGICAL PROCEDURE

Bimedial rectus recessions either alone or in combination with conjunctival recessions, inferior oblique myectomies, or faden sutures were used for the initial operation in 35 patients (87·5%).

The two main groups available for comparison

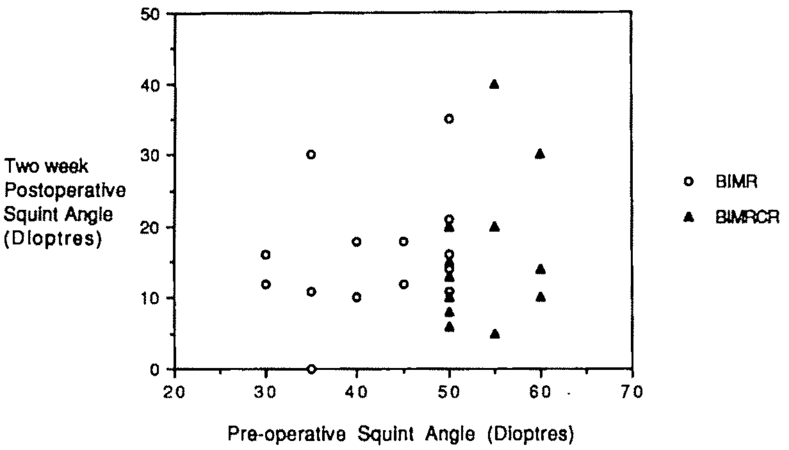

Figure 1 Relationship of the postoperative to the preoperative squint angles in 15 patients undergoing bimedial rectus recessions (BIMR) and 12 patients undergoing bimedial rectus recessions with conjunctival recessions (BIMRCR).

are bimedial rectus recessions of 6 mm without conjunctival recessions (used for preoperative angles of 50 dioptres or less), and bimedial rectus recessions of 6 mm with conjunctival recessions (used for preoperative angles of 50 dioptres or more), both groups being combined with inferior oblique myectomies when required.

A comparison of the postoperative squint angle at 2 weeks in the two groups is shown in Figure 1. An increase in the preoperative squint angle in both groups is associated with an increase in the residual esotropia. For a preoperative angle of 50 dioptres where either procedure was used the group with conjunctival recessions was corrected by a median value of 4·5 dioptres more at first postoperative examination.

Discussion

Looking at the group as a whole, the best results were achieved in the children who had a squint angle within ±15 dioptres of straight at 3–6 months postoperatively. A favourable outcome was present in 19 of 27 (70·4%) of these children compared to four of 13 (30·8%) children with a 3–6 month postoperative squint angle of greater than ±15 dioptres.

Furthermore if this alignment was achieved before the age of 24 months a favourable outcome occurred in nine of 11 children (81·8%). This is in accordance with the findings of Ing who demonstrated an improved outcome for children adequately aligned prior to their second birthday.[3] An added bonus may be the improvement in the child's fine motor development and visual function following surgery.[11]

Amblyopia which persisted at the time of surgery was associated with a lesser percentage (33·3%) of children with a favourable outcome when compared with children whose amblyopia was successfully reversed by the time of surgery (53%). Anisometropia was associated with unreversed preoperative amblyopia. The onset of amblyopia postoperatively in patients not known to be amblyopic preoperatively is well recognised,[12] particularly in those with a residual small angle esotropia; but in our series 66·7% still achieved a favourable outcome following amblyopia treatment.

Inferior oblique overaction, DVD, and latent or manifest latent nystagmus are associated with congenital esotropia. They may occur in combination, and one of our patients demonstrated all three. Inferior oblique overaction and DVD were present in two and latent nystagmus and DVD in three patients. There was no evidence that the presence of these disorders was associated with a less favourable outcome but the numbers of each are too small to allow a definitive statement.

Conjunctival recessions have been shown to augment the results of convergent squint surgery, and this is confirmed in Figure 1, where for equal preoperative squint angles, a greater correction is achieved with augmented or *en bloc* recessions.[7 13] Inferior oblique surgery is not considered to have any significant effect on the postoperative horizontal alignment.[14] The variation in the postoperative result for the same operation for an equal preoperative squint angle is also demonstrated in Figure 1, which increases the difficulty in predicting the outcome of squint surgery in the individual child.

The results suggest that an increase in the amount of surgery for any given preoperative squint angle would be appropriate. Bimedial rectus recessions of 7 mm, which have been shown to be effective and not to cause limitation of convergence or adduction,[15] or the use of conjunctival recessions, should be considered for smaller preoperative squint angles. Measurement from the limbus may be beneficial where maximal medial rectus recession is sought, as the distance of the medial rectus insertion from the limbus is variable.[16]

Conclusion

We have shown that the best prospects for a favourable outcome in congenital esotropia occur with alignment within ±15 dioptres of straight at 3–6 months postoperatively, particularly if this alignment is achieved before the second birthday. Amblyopia which persisted at the time of surgery was associated with anisometropia and with a lesser percentage of children achieving a favourable outcome. More surgery for the larger preoperative squint angles would have been appropriate. A beneficial effect from the use of conjunctival recessions was demonstrated. We therefore recommend early surgery, ideally by 18 months of age, designed to achieve alignment within ±15 dioptres of straight at the 3–6 month examination, and to allow secondary surgery prior to their second birthday for those children not achieving this result. Careful attention must also be directed towards reversing amblyopia and correcting significant anisometropia in the preoperative period.

The authors are grateful to Helen Jones, University Department of Ophthalmology, Birmingham, for statistical advice.

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British Journal of Ophthalmology, 1992, 76, 346–348

Full thickness macular breaks in rhegmatogenous retinal detachment with peripheral retinal breaks

P Riordan-Eva, A H Chignell

Abstract

Between 1975 and 1989, 11 eyes were treated for retinal detachments with both peripheral and full thickness macular breaks. Long term retinal reattachment was dependent on successful closure of peripheral retinal breaks. Direct treatment of the macular break was necessary in only one case, which redetached 3 months after vitrectomy. Vitrectomy is not the initial treatment of choice for uncomplicated retinal detachments with both peripheral and full thickness macular breaks, unless required for the closure of the peripheral retinal breaks.

The relationship between macular breaks and rhegmatogenous retinal detachment is variable. In the highly myopic eye a break arising in the macular region may initiate rhegmatogenous retinal detachment, and in these cases subretinal fluid (SRF) accumulates around the break and extends towards the periphery. In other and usually more complex rhegmatogenous retinal detachments, such as complicating advanced proliferative vitreoretinopathy (PVR), in detachments secondary to vasoproliferative retinopathy, and in detachments associated with trauma, a macular break if present seems to play a secondary rather than an initiating role in the process of detachment.

In a third poorly documented but widely recognised group of apparently uncomplicated retinal detachments, a macular break develops in what had apparently been a normal macula, as a result of spread of SRF from a peripheral detachment initiated by a peripheral retinal break. This report describes our experience of 11 such cases.

Materials and methods

Among the retinal detachments treated between 1975 and 1989 by the Vitreo-Retinal Unit at St Thomas' Hospital, 11 cases of full thickness macular breaks arising secondary to peripheral retinal detachments have been identified. In all cases the break was identified as full thickness by preoperative and postoperative examination, as well as by direct peroperative identification in those eyes treated by vitrectomy. For the macular break to be considered secondary to spread of SRF from a peripheral detachment there had to be either; (i) a clear history of a progressive peripheral field defect, consistent with spread of SRF from identified peripheral retinal breaks (six cases); or (ii) a subtotal retinal detachment in which the SRF distribution was entirely consistent with spread from identified peripheral breaks,[1] and in which there was no suggestion of the macular break preceding the peripheral break (five cases). All cases of macular breaks in which the temporal sequence of peripheral to central retinal detachment was not clearly established were excluded. Eyes with previously abnormal macular function as indicated by reduced vision or documented macular disease, myopia of more than 6 dioptres, history of recent trauma, evidence of vasoproliferative retinopathy, or PVR greater than grade B, were also excluded.

Patient details were obtained from hospital notes and the proforma sheets completed at the time of surgery, which form the basis of the Vitreo-Retinal Unit database. Each patient had undergone standard preoperative assessment, and retinal examination by indirect ophthalmoscopy with scleral indentation and slit-lamp biomicroscopy, including three mirror contact lens examination. Retinal findings had been recorded on standard colour coded retinal charts.

Eleven patients were identified, six male and five female. Ages ranged from 26 to 73 years with a mean age of 61 years. Six eyes were emmetropic and five were myopic (less than 6 dioptres). All eyes were phakic. The macular break retinal detachment was unilateral in all cases. The macular break was always a round hole at the fovea. The fellow eye was normal in nine, affected by mild atrophic macular degeneration in one, and had previously developed a rhegmatogenous retinal detachment without macular break formation in one.

METHODS OF SURGERY

During the collection of these cases, the surgical approach varied because:

(a) it was uncertain if the macular breaks were full thickness, and

(b) the contribution of full thickness macular breaks to rhegmatogenous retinal detachment was unclear.

Initially treatment was directed at closing the peripheral breaks using conventional methods; pars plana vitrectomy (PPV) was only undertaken when conventional surgery had failed to close them. Latterly, PPV was undertaken as a primary procedure if:

(a) it was thought necessary to drain all the SRF to achieve peripheral break closure, in which case this could be performed easily and safely via the macular break and supplemented by postoperative gas tamponade, or

(b) the peripheral breaks were too posterior for easy scleral buckling.

Conventional surgery and pneumatic retinopexy

All eyes treated conventionally underwent

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Accepted for publication
3 February 1992

cryotherapy to peripheral retinal breaks and then local scleral buckling, with or without encirclement, and with or without drainage of SRF. Macular buckling techniques were not used in any case.

Pneumatic retinopexy was performed by cryotherapy to the retinal breaks and then intravitreal injection of C3F8 gas, followed by appropriate posturing.

Pars plana vitrectomy

Pars plana vitrectomy (PPV) was performed using a standard triple port 20 gauge system. In all cases the schlieren phenomenon (direct visualisation of the passage of SRF into the vitreous cavity during aspiration in the vicinity of a retinal break) was used to confirm the presence of a full thickness break at the macula. In no case was it possible, either by direct visualisation or by tugging of the posterior detached retina during vitreous aspiration, to demonstrate vitreous attachment or traction in the macula area. Peripheral retinal breaks were treated with cryotherapy or endolaser photocoagulation. Scleral buckles were used when necessary. In all cases postoperative tamponade was accomplished with a 30% SF6/air mixture injected into the vitreous cavity after drainage of SRF via the macular break. Endolaser to the macular break was only used when specifically indicated.

The configuration of the initial detachment and the surgery undertaken are outlined in Table 1. Follow-up averages 27 months, with only two cases being followed up for less than 4 months from their last surgical procedure.

Results

In all 11 treated eyes the retina was successfully reattached. Final visual acuities ranged from 6/60 to counting fingers.

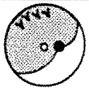
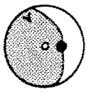
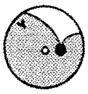
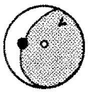
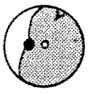
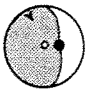
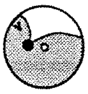
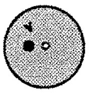
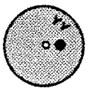
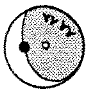
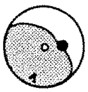
Three eyes (cases 1–3) were treated entirely by conventional surgery, with a total of four procedures. The failure of initial surgery in case 3 was due to inadequate closure of the peripheral break. Among the three eyes (cases 4–6) undergoing vitrectomy after failure of conventional surgery, all the conventional procedures had failed due to missed peripheral breaks, but these could not be identified preoperatively and were found at vitrectomy. In the eye previously treated with two conventional procedures (case 6) endolaser was applied to the macular area at the time of vitrectomy. It was still felt that an open peripheral break was the reason for failure of conventional surgery and this was dealt with accordingly. The macular laser was only applied (probably unnecessarily) as a prophylactic measure against the possibility of redetachment from the macular break.

Among the five eyes treated by primary vitrectomy (cases 7–11), two had peripheral breaks too posterior to allow safe scleral buckling, and in the other three vitrectomy was performed to give access to the macular break for internal drainage of SRF. A total of nine procedures (eight vitrectomies and one pneumatic retinopexy) were required. Inadequate closure of the peripheral breaks was the reason for failure in two out of the three eyes requiring multiple procedures. In only one eye was failure of surgery due to redetachment from the macular break, and this did not occur until 3 months after the initial vitrectomy. It was successfully treated by redraining SRF via the macular break and endolaser to the macula, without any alteration in the scleral buckles.

Discussion

Although there is no previously published study specifically examining the management of rhegmatogenous retinal detachments with both macular and peripheral breaks in eyes without high myopia, preceding trauma, or significant proliferative vitreoretinopathy, the matter has been the source of much discussion. Some authors have felt that treating only the peripheral break is inadequate.[2] whereas others have said

Table 1 Configuration of the initial retinal detachment and details of surgery undertaken

Case no	*Initial configuration*	*Surgery*	*Macular laser*	*Scleral buckle*	*Outcome*
1		Conv (ND)	–	Circ	Flat
2		Conv (ND)	–	Circ	Flat
3		Conv (ND)	–	Radial	Failed
		Conv (D)	–	Radial Encirc	Flat
4		Conv (ND)	–	Radial	Failed
		Vit	No	Circ Encirc	Flat
5		Conv (D)	–	Circ Encirc	Failed
		Vit	No	Circ Encirc	Flat
6		Conv (D)	–	Radial	Failed
		Conv (D)	–	Radial	Failed
		Vit	Yes	Circ Encirc	Flat
7		Vit	No	Encirc	Flat
8		Vit	No	No	Flat
9		Vit	No	Circ Encirc	Redetached
		Vit	No	Circ Encirc	Flat
10		Vit	No	No	Failed
		Pneumo	–	No	Redetached
		Vit	No	Circ Encirc	Flat
11		Vit	No	Radial	Redetached
		Vit	Yes	Radial	Flat

Conv (ND) = conventional surgery without drainage of subretinal fluid
Conv (D) = conventional surgery with drainage of subretinal fluid
Vit = pars plana vitrectomy with internal drainage of subretinal fluid and intraocular gas tamponade
Pneumo = pneumatic retinopexy
Circ = circumferential
Encirc = encirclement

that it is usually sufficient and that the macular break only needs treatment if it is responsible for redetachment.[3,4] The matter is complicated by discussion of the validity of preoperative diagnosis of a full thickness macular break. Possible misdiagnosis was highlighted in a report of retinal detachments preoperatively thought to be associated with a full thickness macular break and treated by surgery to the peripheral break only. Of these as many as 75% had no features of a macular break following reattachment of the retina[5]; such macular breaks have been termed pseudo-holes.[6] The recovery of good vision after surgery casts doubt on the reliability of preoperative detection of full thickness macular breaks, although it has been reported.[7,8]

In our series the demonstration at PPV in eight cases that the macular breaks were indeed full thickness and transmitted SRF made us confident that careful preoperative examination had predicted accurately the presence of a full thickness break in all cases.

The operative findings at PPV gave no obvious clue as to the mechanism of formation of the macular break. There was no sign of vitreomacular attachment or traction, but the same operative techniques have demonstrated vitreous traction in macular hole retinal detachments in high myopes.[9] Moreover, developments in the understanding of the pathogenesis of idiopathic macular holes have clearly shown that more sophisticated operative techniques may be required to detect vitreomacular adhesions.[10] Macular break formation in the cases reported here may have represented an unusual response of the macula to the presence of underlying SRF, although in none of them was there any evidence of pre-existing macular disease.

The successful treatment of three cases by conventional surgery directed purely at the peripheral breaks, and six other cases by vitrectomy and gas tamponade without formation of a chorioretinal adhesion at the macula, demonstrates that macular breaks do not behave like peripheral breaks in the pathogenesis of rhegmatogenous retinal detachment. Whereas failure to seal a peripheral break in detached retina will always prevent retinal reattachment, the change in contour of SRF indicating the site of the open break,[11] the same rule does not apply to macular breaks. When a macular break develops in association with rhegmatogenous detachment from peripheral retinal breaks, it is virtually always only necessary to seal securely the peripheral breaks to achieve lasting retinal reattachment. In only one case in this series was it clearly established that the macular break was responsible for the reaccumulation of SRF after closure of the peripheral breaks, and that direct treatment of the macular break was then required (case 11). This eye had previously been vitrectomised. (Macular laser was used in case 6 as a questionable prophylactic measure only.)

Even in the presence of a full thickness macular break, the primary treatment of uncomplicated rhegmatogenous retinal detachments with peripheral breaks should be directed at closure of the peripheral breaks, which should in itself be enough to achieve lasting reattachment. PPV is useful to allow safe internal drainage of SRF, internal searching for peripheral breaks, postoperative gas tamponade, and closure of posterior breaks without scleral buckling, but there is no evidence that PPV for the sake of direct treatment of the macular break is necessary in the first instance.

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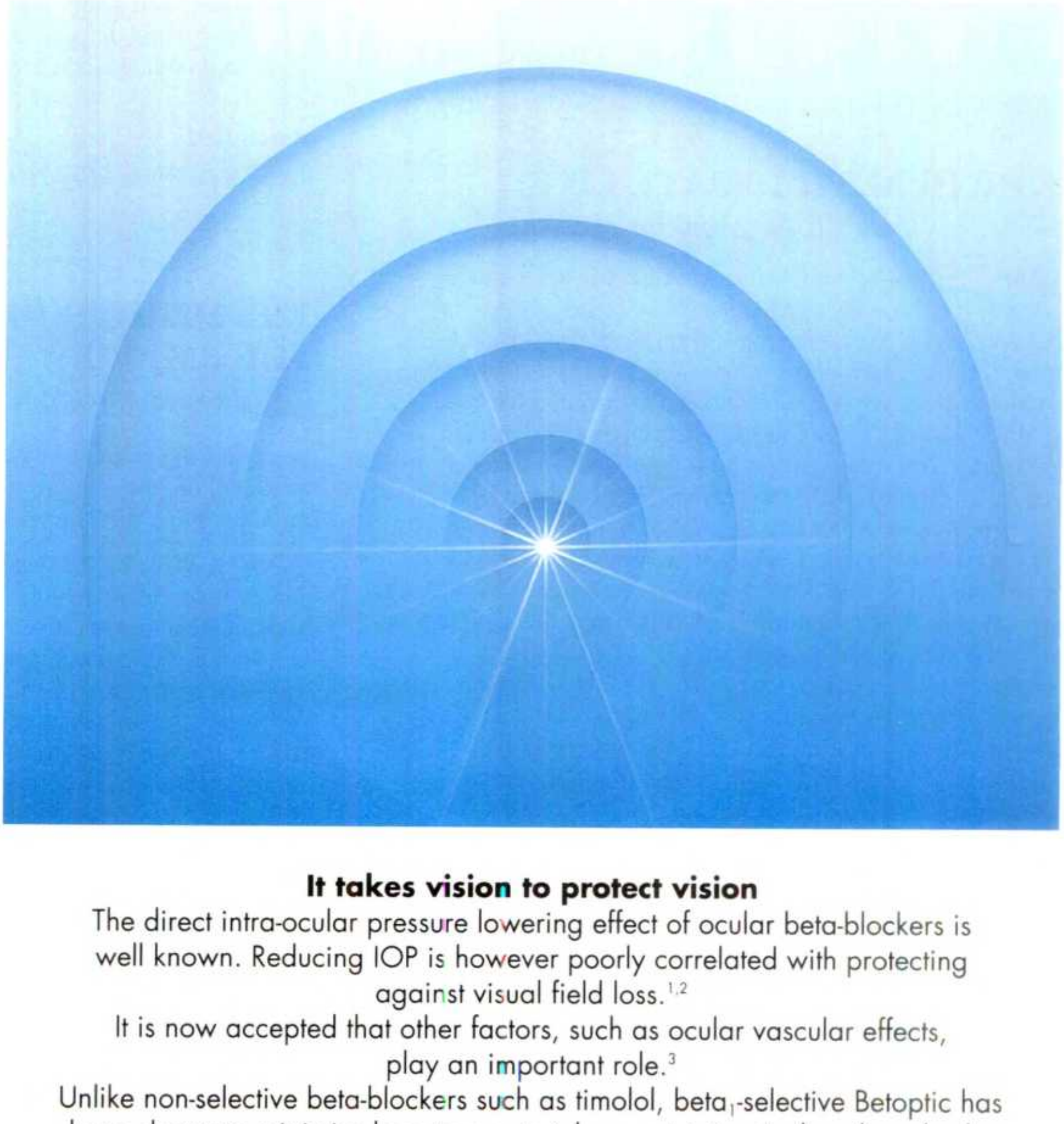

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British Journal of Ophthalmology, 1992, **76**, 349–352

Management of traumatic optic neuropathy – a study of 23 patients

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Accepted for publication
24 October 1991

Abstract

Twenty three patients with traumatic optic neuropathy were managed by medical and surgical treatment as follows. High dose intravenous steroids were initiated in all patients. If visions did not improve significantly after 24 to 48 hours decompression of an optic nerve sheath haematoma by medial orbitotomy and neurosurgical decompression of the optic canal were considered based on computed tomographic scan findings. Nine of 16 patients who received steroids only showed significant improvement. One of three showed improvement on optic nerve decompression after steroid failure; three or four showed improvement with combined optic nerve sheath decompression by the medial orbitotomy and decompression of the optic canal by frontal craniotomy. A lucid interval of vision after injury and an enlarged optic nerve sheath were associated with an improved prognosis. Five of the 23 patients had a lucid interval and all five had a final improved vision, while only five of 18 patients without a lucid interval improved. Similarly seven of the nine with an enlarged optic nerve sheath showed improvement while only three of 10 patients (three bilateral cases) who presented with no light perception improved with medical and surgical treatment. While a prospective controlled study of the management of traumatic optic neuropathy is necessary this preliminary study suggests that treatment of traumatic optic nerve sheath haematoma by optic nerve sheath decompression should be considered in selected patients.

Although the natural history of traumatic optic neuropathy is unknown recent studies suggest that high dose steroids, and even surgical decompression of the optic canal, may restore vision in selected patients.[1-7] While visual recovery after decompression of an enlarged optic nerve sheath due to traumatic haemorrhage has been reported this treatment has received little attention in the literature.[8-11] The results of 23 patients who received high dose steroids and underwent decompression of the optic nerve sheath and the optic canal are presented.

Patients and methods

All patients in this series had loss of vision after trauma wth an afferent pupillary defect in the involved eye and were treated within the first 48 hours of injury. According to the protocol at UMD-NJ Medical School, a regional trauma centre, all patients received a complete ophthalmic examination by one of us. Patients with penetrating ocular injuries or optic nerve avulsion were excluded from the study. All patients received an initial 1 g loading dose of Solu Medrol (methylprednisolone) and then 250 mg intravenously every 6 hours for 72 hours after medical clearance by the trauma team. Patients with increased intraorbital pressure due to haemorrhage were treated by emergency lateral canthotomy with drainage of subperiosteal or intraorbital haemorrhage. High resolution brain and orbital computed tomography (CT) scans were obtained while treatment was instituted. Thin 1·5 cm sections through the intraorbital and intracanalicular optic nerve were obtained to define 'surgically treatable pathology'; enlarged optic nerve sheath with presumed intrasheath haemorrhage; or narrowing of the optic canal or orbital apex by bone spicules. If vision improved

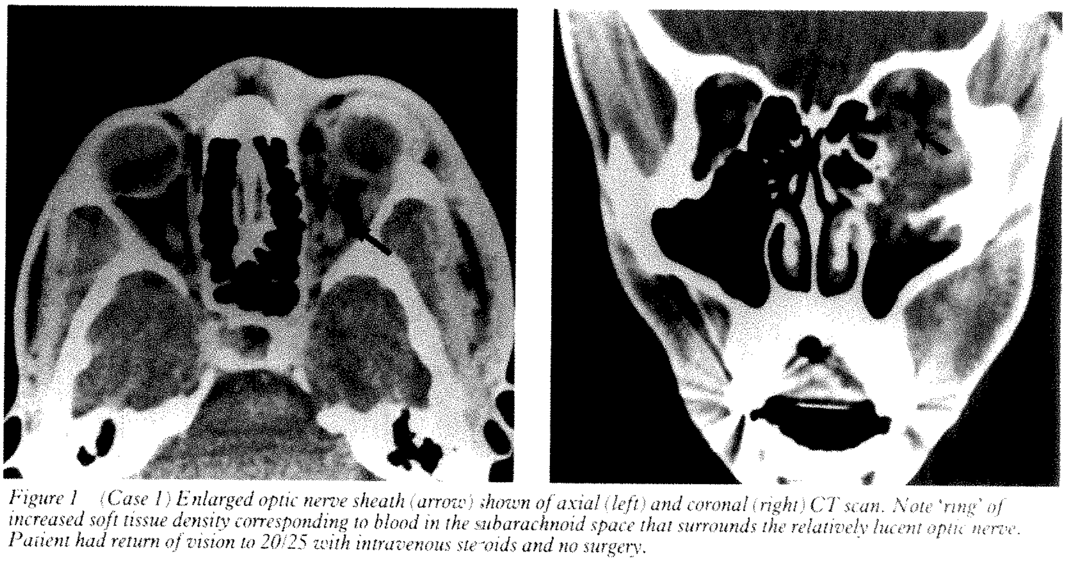


Figure 1 (Case 1) Enlarged optic nerve sheath (arrow) shown of axial (left) and coronal (right) CT scan. Note 'ring' of increased soft tissue density corresponding to blood in the subarachnoid space that surrounds the relatively lucent optic nerve. Patient had return of vision to 20/25 with intravenous steroids and no surgery.

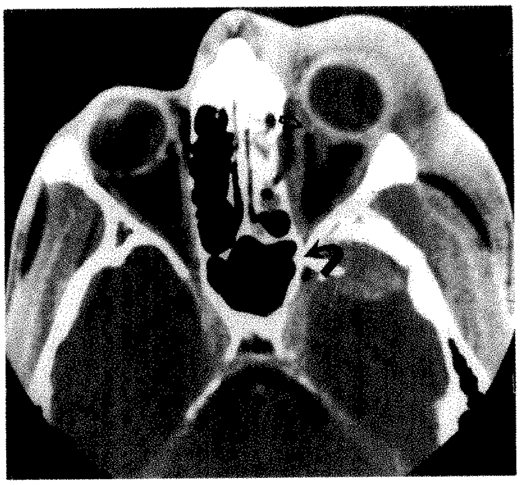


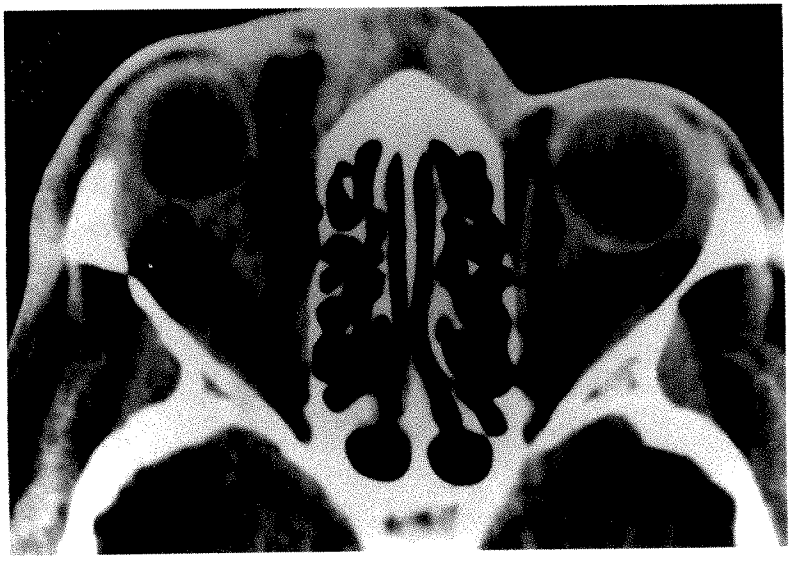
Figure 2 (Case 23) Lateral wall impinges on orbital apex (curved arrow). The retrobulbar portion of the nerve appears thickened (straight arrows). Patient underwent elevation of the lateral wall of the orbit and craniotomy with decompression of the root of the optic canal. The optic nerve was markedly shrunken at the level of the canal; the sheath contained a paste-like substance. The patient had no return of vision.

over the first 24 to 72 hours steroids were continued for a total of 5 to 7 days and were then tapered. If vision did not improve after 24 to 72 hours of steroids decompression of an optic nerve sheath by medial orbitotomy and decompression of the optic canal with removal of apical orbital bone fragments by frontal craniotomy were considered if on CT scan: (1) the optic nerve sheath appeared enlarged by presumed intrasheath haemorrhage; or (2) the optic canal or optic nerve at the orbital apex appeared compressed by bone spicules (Figs 1–3). If vision did not improve and no 'surgically treatable pathology' was present on CT scan steroids were gradually tapered after 3–4 days. Patients with medical problems and, early in the study, those with unilateral involvement were not always considered surgical candidates.

SURGICAL TECHNIQUE

In all patients the decompression of the optic nerve sheath was performed by a conjunctival approach under general anaesthesia similar to that described for pseudotumour cerebri.[12,13] A 270 degree conjunctival peritomy was performed. The superior and inferior rectus muscles were isolated on 4–0 silk traction sutures. The medial rectus muscle at its insertion was sutured with a double armed 5–0 vicryl suture that was locked at each edge of the muscle; the muscle was then cut at its insertion and detached from the globe as if a standard muscle recession were to be performed. The two free arms of the vicryl suture were taped without tension with a 1/4 inch steri-strip to the patient's brow and cheek on the opposite side. Care was taken to avoid traction and damage to the medial rectus muscle. Multiple running bites were taken through the stump of the muscle with a 4–0 silk traction suture. A Schepens retractor or thin ribbon retractor was placed in the medial orbit between the globe and the medial rectus muscle. Cottonoids, cotton tip applicators, and suction facilitated exposure of the optic nerve sheath through the operating microscope. A no 11 blade was used to make three 2–3 mm longitudinal incisions into the nerve sheath away from superficial blood vessels. The medial rectus muscle was resutured into position after the traction sutures were removed and the conjunctival peritomy closed.

Figure 3 (Case 19) Axial CT scan shows enlarged nerve (arrows) due to sheath haematoma behind globe.



The neurosurgical procedure was then performed through a coronal flap by the neurosurgeons (AK, MS). The optic canal was unroofed and any bone spicules that impinged on the nerve were removed. All patients continued to receive steroids for 72 hours after surgery. For those with improvement in vision after surgery the steroids were continued for a total of 5 to 7 days and then tapered.

Results

SURGICAL FINDINGS

At surgery a swollen haemorrhagic nerve sheath was identified in three of the seven patients and a clear yellowish fluid was recovered after the incision into the nerve sheath. In patient no 17, no blood or fluid was recovered at the time of the optic nerve sheath decompression yet the vision returned to 20/25.

Case no 23 presented with NLP vision; the entire lateral wall of the orbit was displaced posteromedially against the optic nerve (Fig 2). At the time of neurosurgical decompression of the optic nerve at the optic canal the nerve sheath was filled with a whitish pink paste.

VISUAL RECOVERY

Nine of 16 patients showed significant improvement on steroids alone; seven (case nos 1–6, 10) of the nine who showed improvement had an enlarged optic nerve sheath (Table 1). Case nos 12 and 16 had no significant pathology on CT scan. Three of the nine patients required immediate bedside canthotomy prior to treatment with steroids for increased intraorbital pressure. Of the seven patients (case nos 7, 8, 9, 11, 13–15) who had no improvement on steroids six presented with no light perception (NLP) and one with LP (case no 9) in the involved eye. Three patients (case nos 7–9) with optic nerve sheath haematoma and two patients (case nos 13, 15) with optic canal fractures did not have surgery for a variety of reasons including medical contraindications.

One of three patients who did not respond to

Table 1 Patients with traumatic optic neuropathy treated with steroids alone

Case no/age/sex	*Type of injury*	*Initial/final vision*	*CT finding*
1. 26, M	Blunt trauma, bat	CF 2 ft/20/25	Optic nerve sheath haematoma
2. 44, M	Blunt trauma	20/70–2/20/20–2	Optic nerve sheath haematoma
3. 15, M	Fall from bicycle	CF 1 ft/20/400	Optic nerve sheath haematoma
4. 27, M	Blunt trauma	20/200/20/40	Optic nerve sheath haematoma
5. 18, M	Motor vehicle accident	CF 2ft/20/30	Optic nerve sheath haematoma
6. 58, M	Sinus endoscopy, surgery	CF 3 ft/20/25	Optic nerve sheath haematoma
7. 42, M	Blunt trauma, fist	NLP/NLP	Possible optic nerve sheath haematoma
8. 13, M	Knife to orbit	NLP/NLP	Optic nerve sheath haematoma
9. 90, M	Motor vehicle accident	LP/LP	Optic nerve sheath haematoma Possible optic nerve avulsion
10. 54, M	Blunt trauma	CF 3 ft/20/20	Optic nerve sheath haematoma, left tripod fracture
11. 27, M	Gunshot right orbit	NLP/NLP	No significant pathology*
12. 53, M	Motor vehicle accident	20/400/20/25	No significant pathology
13. 36, M	Fist	NLP/NLP	Apical medial optic canal fracture
14. 27, M	Gunshot left orbit	NLP/NLP	No significant pathology
15. ?, M	Motor vehicle accident	NLP/NLP	Optic canal fracture
16. ?, M	Blunt trauma	20/800/20/40	No significant pathology

*Central retinal artery occlusion.
CF=counting fingers, NLP=no light perception, LP=light perception.

Table 2 Characteristics of patients with traumatic optic neuropathy treated with steroids and optic nerve sheath decompression

Case no/age/sex	*Type of injury*	*Initial/final vision*	*CT finding*
17. 28, M	Knife to orbit	CF 1 ft/20/25	Optic nerve sheath haematoma
18. 18, M	Gunshot to orbits	Bilateral NLP/NLP	Right optic nerve sheath haematoma*
19. 27, M	Motor vehicle accident	NLP/NLP	Right optic nerve sheath haematoma

* Left optic nerve avulsed and not treated; right optic nerve sheath haematoma decompressed.

*Table 3 Characteristics of patients with traumatic optic neuropathy treated with steroids, optic nerve sheath decompression, and neurosurgical decompression of the optic canal**

Case no/age/sex	*Type of injury*	*Initial/final vision*	*CT finding*
20. 12, M	Gunshot to orbits	NLP both eyes/NLP OD 20/200 OS	Right optic nerve avulsion, left optic nerve sheath haematoma with bone spicules at orbital apex
21. 32, M	Gunshot to orbits	NLP both eyes/NLP OD HM OS	Right optic nerve avulsion, left optic nerve sheath haematoma with bone spicules at orbital apex
22. 34, F	Motor vehicle accident	NLP both eyes/ improved pupillary reaction both eyes†	Left optic nerve sheath haematoma, bilateral optic canal fracture
23. 28, M	Blunt trauma	NLP/NLP	Optic nerve sheath haematoma, apical bone directly impinging on optic nerve

* In each case finding on CT was treated surgically. Patients with presumed avulsion were not treated.
† Unable to assess exact vision due to mental status after injury.
HM=hand movements.

steroid treatment showed improvement on optic nerve sheath decompression by medial orbitotomy of an enlarged sheath (Table 2).

Three patients who did not respond to steroids had optic nerve sheath decompression; one of the patients improved to 20/25 (case no 17) (Table 2). Four patients who did not respond to steroids had combined optic nerve sheath decompression and neurosurgical decompression of the optic canal; three showed improved vision (Table 3).

All five patients with a lucid interval of vision after the injury had a final improved vision while only five of 16 patients without a lucid interval improved. Seven of 10 patients (three bilateral cases) who presented with NLP had no improvement with any treatment. Three (four eyes) of the 10 with improvement had combined optic nerve sheath decompression and neurosurgical decompression of the optic canal.

No medical or surgical complications occurred in this series of 23 patients.

Discussion

The present data suggest the efficacy of steroids and possibly surgery in selected patients with traumatic optic neuropathy. All 23 patients initially received high dose steroids. Nine of 16 patients showed significant improvement on steroids without surgery. In patients without visual improvement after 24 to 48 hours of intravenous steroids surgery was considered if: (1) an enlarged optic nerve sheath with presumed intrasheath haemorrhage decompression of the retrobulbar portion of the optic nerve sheath, or (2) a narrowed optic canal or orbital apex by bone spicules were present on CT scan. To date the role of optic nerve fenestration in the treatment of traumatic optic neuropathy has not been clearly elucidated.[8-10]

One of three patients showed visual improvement after optic nerve sheath decompression. Three of four showed improvement with combined optic nerve sheath decompression and neurosurgical decompression of the optic canal by neurosurgical frontal craniotomy. One patient despite such combined surgery showed no improvement in vision. Decompression of the optic canal may alternatively be performed by medial orbitotomy with a skin incision or by a transantral approach.[2 14-16] The latter approach may have less morbidity than a craniotomy; however there were no complications in this series and frontal craniotomy allows complete decompression of the optic canal and removal of apical orbital bone fragments.

Optic nerve sheath haematomas are relatively rare and are difficult to demonstrate radiographically. For these reasons there are only a few reported cases of decompression of an enlarged optic nerve sheath.[8-11] In this series fluid was not always recovered at the time of optic nerve sheath decompression and in one such patient (case no 17) the final vision was 20/25. The findings may be due to (1) oedema that involves the entire nerve and not just the subarachnoid space, or (2) the collection of blood may be focal away from the surgical site. Magnetic resonance imaging may be helpful in localising blood.

The natural history of traumatic optic neuropathy is unknown, and even the exact mechanism by which corticosteroids reduce optic nerve injury is unclear.[1-7] The rationale for treatment is as follows. Steroids probably decrease the intraneural or extraneural oedema and relieve compression of the nerve fibres.[4] By reducing vasospasm steroids may also limit contusion necrosis of the nerve.[5]

The effect of steroids on the resorption of an optic nerve sheath haematoma is also unclear. Surgical evacuation of non-resorbing nerve sheath haematoma should be considered when initial treatment with steroids fails to improve vision.[8-11] Timely surgical optic nerve sheath decompression is initiated in order to avoid irreversible damage to the axons of the optic nerve compressed by the subarachnoid blood within the swollen nerve sheath.

The data show that a favourable prognosis is associated with (1) a lucid interval, and (2) an enlarged optic nerve sheath. All five patients with a lucid interval of vision after the injury had a final improved vision. Seven of the nine who showed improvement with steroids had an enlarged optic nerve sheath. Poor prognosis is associated with (1) initial NLP vision, (2) no lucid interval, and (3) displacement of large bone fragments against the optic nerve (case no 23). Seven of 10 patients (three bilateral cases) who presented with NLP had no improvement with any treatment. Only five of 15 patients who did not have a lucid interval ultimately improved.

Patients who present without a lucid interval and with NLP vision should be evaluated and treated. In the three patients (case nos 20–22) who presented with NLP and subsequently improved, the final vision was 20/200, hand motions, and indeterminable in the third patient due to intracranial injuries. The latter patient had bilaterally improved pupillary responses.

In summary optic nerve sheath decompression alone or combined with decompression of the optic canal may be indicated in selected patients who fail to respond to high dose intravenous steroids. The definitive role of surgery in the management of traumatic optic neuropathy remains unclear until a protocol is adopted on a multicentre level. Initiation of steroids for 24 to 48 hours affords sufficient time for consultations, radiological studies, and conference with the patient and family prior to any surgical intervention.

Presented in part at the Annual Meetings of the American Society of Ophthalmic, Plastic and Reconstructive Surgery, New Orleans, Louisiana, 28 October 1989 and Anaheim, California, 12 October 1991. The work was supported in part by an unrestricted ophthalmology departmental grant from Research to Prevent Blindness, New York, New York.

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British Journal of Ophthalmology, 1992, 76, 353–357

Modification of trabeculectomy to avoid postoperative hyphaema. The 'guarded anterior fistula' operation

A G P Konstas, J L Jay

Abstract

The effect of varying the position of a trabeculectomy fistula on the rate of postoperative hyphaema was studied in a prospective randomised trial. One eye of each of 78 consecutive patients with primary open angle glaucoma and exfoliation glaucoma was allocated to one of two groups. In group A the fistula was fashioned anterior to the scleral spur, entirely in corneal tissue. In group B the fistula included cornea and sclera with trabecular meshwork and scleral spur. Seven out of 39 eyes (18%) in group A developed a postoperative hyphaema with detectable blood level, compared with 22 out of 39 eyes (56%) for group B ($p<0\cdot001$). In addition, the severity of the bleeding was greater in group B, and the three cases of recurrent bleeding were all in this group. Group B patients remained in hospital for an average of 3·9 days, which was significantly longer ($p=0\cdot004$) than the average of 2·9 days for group A. This difference was related to the frequency and severity of the hyphaema. The type of dissection or the occurrence of hyphaema did not influence the intraocular pressure at 4 months after surgery.

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Accepted for publication
21 November 1991

Trabeculectomy is the standard drainage operation for primary open angle glaucoma.[1-4] Its main advantage over full thickness drainage procedures is a reduced incidence of complications.[5-8] The success and safety of the procedure have been established,[9-12] so that recently there has been a tendency towards earlier surgery.[13-15]

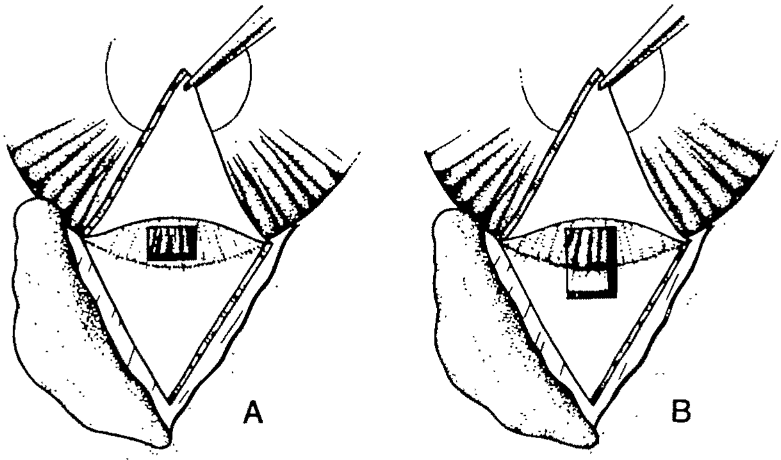

Figure 1 Schematic drawing of the area of tissue excised to fashion the fistula. In group A the dissection was anterior to the scleral spur and included only corneal tissue. Group B had excision of corneal and scleral tissue incorporating scleral spur and trabecular meshwork.

Nevertheless, operation may be delayed because of fears that there may be surgical complications. The frequency of postoperative hyphaema varies from 15 to 53%,[16-22] and though it is seldom a serious complication it may prolong the patient's stay in hospital. It may also cause temporary reduction in vision, which may be a serious handicap if vision is poor in the other eye. We therefore designed this study to confirm and quantify our observation that excising the inner block anterior to the scleral spur reduced the frequency of postoperative hyphaema.

Patients and methods

A randomised prospective trial was set up to study first trabeculectomies for primary open angle glaucoma and exfoliation glaucoma (alternatively referred to as pseudoexfoliation glaucoma). One eye of 78 consecutive patients operated on between October 1989 and November 1990 was randomly allocated to either group A or group B by means of a table of random numbers. The allocation was identified from the code by the senior operating theatre nurse at the start of the operation, and 13 surgeons took part. Group A had the inner block fashioned and excised entirely anterior to the scleral spur so that only corneal tissue was excised (Fig 1). Group B had a conventional inner block of corneoscleral tissue extending posterior to the scleral spur with the trabecular meshwork near the centre of the excised tissue.[2,4] Nine other patients with primary open angle glaucoma who underwent a trabeculectomy during the course of the trial were excluded. The reasons were failure to allocate a randomisation (two), reluctance of the surgeon to take part (four), other reseach requirements (three).

All degrees of severity of glaucoma were included in the trial, irrespective of level of intraocular pressure, visual field loss, optic disc cupping, or duration of medical treatment. Patients with closed angle glaucoma, secondary glaucomas, previous ocular surgery, and concurrent ocular inflammation were excluded. Eighteen patients undergoing combined extracapsular cataract extraction and trabeculectomy were also excluded from this study. All patients were examined preoperatively according to a predetermined protocol. The following information was recorded: sex, age, diabetes mellitus, arterial hypertension, haematological disorders, reason for diagnosis, and details of glaucoma at time of diagnosis (intraocular pressure without treatment, cup to disc ratio, and visual field). The same glaucoma details at the time of operation (including the intraocular pressure on medical therapy) were recorded together with the time from diagnosis to operation. The indication for surgery (uncontrolled intraocular pressure, progression of visual field loss, both, intolerance to medications, and poor compliance) was also noted. The visual field loss was graded according to the classification by Jay and Murray.[14] All patients were examined by slit-lamp biomicroscopy and gonioscopy prior to surgery for the presence of exfoliation.

The operations were performed under local or general anaesthesia. Following the insertion of a superior rectus suture, a flap of conjunctiva and Tenon's capsule was reflected as shown in Figure 1. A rectangular or triangular half-thickness outer scleral flap was fashioned measuring approximately 4×4 mm. The edges of this flap were not extended into the cornea beyond the limbus. The inner block was dissected as described above according to the random allocation. A peripheral iridectomy was performed in all cases, and the superficial flap was sutured with one to three sutures. The conjunctiva was closed with continuous or interrupted sutures. Viscoelastic substances were not used.

To ascertain the accuracy of dissection with respect to the scleral spur the surgical specimen was fixed immediately after excision in buffered glutaraldehyde 2·5%. The dimensions of the excised tissue were recorded, and all specimens were examined with a dissecting microscope at a ×50 magnification. Where doubt still existed as to the location of the dissected block, paraffin histology was used for confirmation. Similar histological confirmation was carried out in a random 25% sample of all specimens. If any part of the scleral spur or trabecular meshwork was found in the specimens from group A, the case was reclassified as group B (posterior dissection). Similarly, inability to demonstrate anatomical structures consistent with the excision of a posterior block (scleral spur, part of the outflow system) in a specimen from group B led to its transfer to group A. The name of the surgeon was recorded together with his comments as to whether there had been bleeding into the anterior chamber.

Postoperatively patients were examined every day while in hospital, and the following information was recorded: depth of the anterior chamber; hyphaema (*grade 1* – diffuse without formation of blood level; *grade 2* – up to 1 mm; *grade 3* – more than 1 mm), blood clot and other problems. The duration of hyphaema and stay in hospital were noted. Patient details were recorded 3 to 7 days after discharge and again about 6 to 8 weeks later. The final assessment was made approximately 4 months after the operation. The intraocular pressure was recorded after exclusion of possible steroid response at least 2 weeks after discontinuation of steroid eye drops[23] and without supplementary medical treatment. The reason for beginning any supplementary medical treatment after the operation was also recorded. We analysed results for the whole study population and in addition examined separately the results for those patients with exfoliation glaucoma.

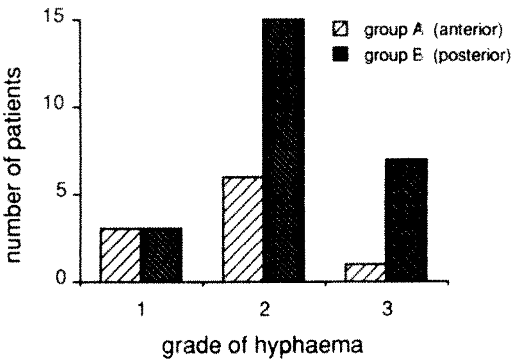

Figure 2 Frequency and severity of postoperative hyphaema. Grade 1, diffuse; grade 2, 0·2–1 mm; grade 3, greater than 1 mm. Anterior dissection (group A) produced significantly fewer hyphaemas, and those which occurred were less severe. There were 39 eyes in each surgical group.

Table 1 Details of patients. There was no statistical difference between the study groups for the features indicated

	n	*Mean age*	*Male/female ratio*	*Arterial hypertension*	*Diabetes mellitus*	*Thrombocytopenia*
Group A	39	68·6 (10·4)	20/19	12	1	0
Group B	39	67·7 (9·1)	21/18	7	1	1

Standard deviations in parentheses.

Table 2 Details of glaucoma features at diagnosis and at the time of operation, with duration of preoperative medical therapy. The groups were not statistically different

		At diagnosis			*At time of operation*	
	n	*Mean IOP (untreated, mm Hg)*	*C/D ratio*	*Duration of medical treatment (months)*	*Mean IOP (treated, mm Hg)*	*C/D ratio*
Group A	39	31 (9·6)	0·6 (0·2)	39·7 (59)	25·9 (6·9)	0·6 (0·1)
Group B	39	29 (9·4)	0·6 (0·2)	27·9 (32)	24·9 (6·3)	0·7 (0·1)

Standard deviations in parentheses.

Differences between the groups were analysed by the two-sample *t* test , the χ^2 test, analysis of variance, and the Mann-Whitney U test where appropriate. Values of p of 0·05 or less were considered to be significant.

Results

All patients were Caucasians, and each group comprised 39 eyes of 39 patients. The patient characteristics for the two groups are shown in Table 1. There was no significant difference between the two groups (A and B) for sex, age, reason for diagnosis, and presence of systemic diseases (arterial hypertension, diabetes mellitus, haematological disorders). Table 2 shows the glaucoma status. At diagnosis there was no difference between the groups for intraocular pressure without medication, cup to disc ratio, prevalence of exfoliation, and duration of medical treatment. Similarly, there was no difference at the time of surgery for intraocular pressure with medication and cup to disc ratio. Neither was there any significant difference for severity of visual field loss at diagnosis and at time of surgery, or for indication for surgery (early trabeculectomy; failed medical treatment).

Twenty nine patients had their operation performed by three consultants, 12 by two senior registrars, and 37 by eight registrars. There was no bias for any level of seniority in the two groups.

In each group two patients were found to have

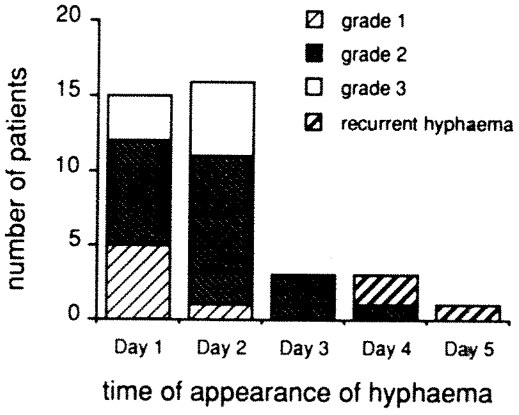

Figure 3 Time of appearance of postoperative hyphaemas of different severity.

tissue specimens which did not correspond with the intended style of dissection, and these two patients were reclassified according to the histological findings. For the main analysis this histologically confirmed classification was used, but no significant difference in results was found between the histological classification and the classification based on the surgeon's intended dissection.

The frequency and severity of hyphaema in the two groups is shown in Figure 2. Thirty five patients (45%) developed a hyphaema: six patients diffuse with no blood level, 21 with a level of 0·2 mm to 1 mm, and eight with more than 1 mm blood level. There was no difference in the frequency of grade 1 hyphaemas (three patients in both groups). Group B had a significantly higher incidence of hyphaemas of both grade 2, 0·2 mm to 1 mm height (15 patients versus six in group A, $p<0\cdot05$) and grade 3, more than 1 mm height (seven patients versus one in group A, $p<0\cdot01$). If only hyphaema severe enough to form a detectable blood level is considered, there were seven out of 39 eyes (18%) in group A, compared with 22 out of 39 eyes (56%) in group B. The difference was statistically significant ($p<0\cdot001$).

The time of occurrence of hyphaema was analysed for the three grades of hyphaema (Fig 3). We disregarded the few circulating red blood cells which were present in the anterior chamber on the first day in nearly every case. Most hyphaemas of grade 1 (five out of six) were present on the first postoperative day, whereas only seven of 21 grade 2 and three of eight grade 3 hyphaemas were present on day one. Grade 1 was therefore significantly different from grades 2 and 3 in that respect. In the latter grades most hyphaemas appeared on the second (13/29) and third (5/29) postoperative day, with only one hyphaema (grade 2) appearing on day four.

Patients with hyphaema stayed significantly longer in hospital: mean, 4·4 days (SD 2·2), than those without: mean, 2·5 days (SD 0·5). Time in hospital was found to be related to the severity of hyphaema. Analysis showed that mean hospital stay for grade 1 hyphaema did not differ from grade 2 (3·2 days and 3·6 days respectively), but grade 3 patients stayed in hospital significantly longer, mean 7·7 days (SD 2·1). When compared with patients without hyphaema, those with both grade 2 and 3 stayed significantly longer in hospital, but grade 1 did not. Overall, group A patients remained in hospital for an average of 2·9 days (SF 1·3), compared with an average of 3·8 days (SD 1·9) for group B. The difference was significant (Mann-Whitney test, $p=0\cdot004$).

Patients with each of the three grades of hyphaema were compared with each other and with those without hyphaema to determine possible distinguishing features. Patients with hyphaema were similar to those without hyphaema with regard to age, sex, systemic diseases, intraocular pressure at diagnosis, cup to disc ratio at diagnosis, intraocular pressure at the time of surgery, and duration of medical treatment.

Out of the 15 patients with exfoliation glaucoma included in this study five (33%) developed a hyphaema postoperatively. There was no case of a severe or recurrent hyphaema. There were seven patients in group A and eight in group B who had exfoliation. In group A one of the seven patients had a diffuse hyphaema (grade 1) compared with one diffuse (grade 1) and three grade 2 hyphaemas in the eight exfoliation glaucoma patients in group B.

With reference to the individual analysis of the three grades of hyphaema, the only significant difference observed was in the sex distribution of grade 1 when compared with grade 2 (5:1 female to male ratio in grade 1 versus 6:15 for grade 2). However, there was no difference in the sex distribution between grades 1 and 3 and 2 and 3. Three patients, all of them in grade 3, experienced recurrent hyphaemas, two of them on the fifth postoperative day and one on the fourth day. These recurrent hyphaemas were of moderate degree, up to 2·5 mm in height, occurred prior to the complete resolution of a pre-existing hyphaema grade 3, and they were not detrimental to the final visual acuity of these three patients.

The two groups, A and B – that is, anterior and posterior dissection and the patients with and without hyphaema – were compared with regard to immediate postoperative complications (anterior chamber depth, uveal effusion, and pain). No eyes required reoperation to correct surgical complications. There was no significant difference between the two randomised surgical groups and between the patients with and without hyphaema.

At approximately 4 months after the operation the final outcome was analysed with regard to reduction of visual acuity, final untreated intraocular pressure, rate of postoperative steroid response, and bleb morphology. One patient was lost to follow-up and one patient did not have sufficient follow-up. Both patients were in group A. No significant difference was noted between groups A and B or between those with hyphaema and those without. The untreated mean intraocular pressure was similar for group A, 15 mm (SD 4·1), and group B, 14·9 mm (SD 5·5). Similarly, the untreated intraocular pressure at 4 months of patients who had hyphaema, 15·7 mm (SD 5·3), was not significantly higher than that of the patients who did not experience a hyphaema, 14·2 mm (SD 4·1) ($p=0\cdot18$).

Examination of individual cases in which the intraocular pressure remained controlled after the operation only with the aid of medical therapy showed them to be distributed evenly between groups A and B and between those with and without hyphaema. Three patients in group A (8%) and four patients in group B (10%) required supplementary medical therapy (one medication each). Similarly, from the hyphaema group three patients (8·5%) required supplementary treatment compared with four patients (10%) in the no-hyphaema group. One patient from group B with a grade 2 hyphaema suffering from thrombocytopenia was the only patient with uncontrolled intraocular pressure, despite medical therapy, after surgery.

Discussion

This prospective randomised study confirms the hypothesis that excision of the inner block anterior to the scleral spur is associated with a significant reduction in the incidence and severity of postoperative hyphaema. The two groups of patients were comparable, the only difference being the mode of dissection of the inner block. Group B, posterior dissection, was associated with the majority of the more severe hyphaemas (grade 3) and with all the recurrent hyphaemas.

The anterior dissection method (group A) should not be confused with 'Cairns-type' trabeculectomy.[1] Cairns excised trabecular meshwork up to the scleral spur and therefore was likely to have disturbed it in at least some cases. Our anterior dissection (guarded anterior fistula) is further forward and excises only cornea, all anterior to the angle structures.

The incidence of hyphaema in our study (45%) is among the higher values quoted in the literature.[3 4 16 18 19 22] This is not surprising, as our figure includes diffuse hyphaemas (six) and small hyphaemas that might have been overlooked in retrospective studies. Watkins and Brubaker[7] found a similar incidence of hyphaema (43%) in the partial thickness group of their study which compared prospectively partial-thickness and full-thickness filtration procedures.

Most diffuse hyphaemas, grade 1, appeared in the first postoperative day. This suggests that in most cases they represent resolving peroperative bleeding. This is not the case with grades 2 and 3, which appear later and are probably new events.

The anterior dissection, which removes only corneal tissue (guarded anterior fistula), is associated with a significantly lower incidence of postoperative bleeding. This suggests that the vascular components of sclera and the ciliary body are the most likely sources of hyphaema. This coincides with our occasional postoperative observation of blood streaming from the fistula site into the aqueous. It is also conceivable that in the dissection of the posterior block and peripheral iridectomy may be closer to the iris root. This study cannot, however, identify with certainty the source of postoperative hyphaema.

It is interesting to note that, although exfoliation glaucoma cases are known to have a varied degree of iris vasculopathy,[24-26] this did not result in a higher frequency of bleeding. The number of patients with exfoliation glaucoma is too small for valid statistical analysis, but the overall incidence of hyphaema and the protective effect of anterior dissection were similar to that for the patients with primary open angle glaucoma.

The intraocular pressure attained with both methods of inner block dissection was similar and within the range quoted in the literature.[4 14 16 17 20 22] Our study confirms that varying the size and site of the fistula does not affect the final intraocular pressure.[27 28] Reduction of the filtration area (anterior dissection) did not influence the final outcome. It has been suggested that hyphaema might affect drainage.[21] We found no significant difference in the surgical outcome (untreated mean intraocular pressure at 4 months) between patients with hyphaema and those without.

It is unlikely that the shape of the outer scleral flap would influence the result. We have gradually increased the use of triangular flaps over the last 10 years without alteration in the rate of either intraocular pressure control or complications, including hyphaema and shallow anterior chamber.

The main advantage of a modified dissection of the inner block is the lower incidence of postoperative hyphaema. This complication sometimes causes alarm to the patient and the surgeon and can influence the duration of hospital stay of the patient. In our study hyphaemas (grades 2 and 3) were associated with a significantly longer hospital stay, and so following the anterior dissection method should reduce costs. The extra cost of longer hospital stay after a trabeculectomy has recently been quantified.[29]

We are grateful to Professor William R Lee for assistance with the histological confirmation, Drs David Keating and Weng Sehu for assistance with statistical analysis, Ms Susan Lang for the illustration, sister Pauline Dabydeen for the randomisation, and all surgeons that took part in the study. This study was supported by a grant from the Alexander von Humboldt Foundation.

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British Journal of Ophthalmology, 1992, 76, 358–364

Microwave plaque thermoradiotherapy for choroidal melanoma

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Abstract

Microwave thermoradiotherapy was used as a primary treatment for 44 patients with choroidal melanoma. An episcleral dish-shaped microwave antenna was placed beneath the tumour at the time of plaque brachytherapy. While temperatures were measured at the sclera, the tumour's apex was targeted to receive a minimum of 42°C for 45 minutes. In addition, the patients received full or reduced doses of plaque radiotherapy. No patients have been lost to follow-up. Two eyes have been enucleated: one for rubeotic glaucoma, and one for uveitic glaucoma. Though six patients have died, only one death was due to metastatic choroidal melanoma (39 months after treatment). Clinical observations suggest that the addition of microwave heating to plaque radiation therapy of choroidal melanoma has been well tolerated. There has been a 97·7% local control rate (with a mean follow-up of 22·2 months). We have reduced the minimum tumour radiation dose (apex dose) to levels used for thermoradiotherapy of cutaneous melanomas (50 Gy/5000 rad). Within the range of this follow-up period no adverse effects which might preclude the use of this microwave heat delivery system for treatment of choroidal melanoma have been noted.

Heat has been shown to potentiate radiation in the treatment of cancer.[1-6] This is because hyperthermia can directly kill cells, it can inactivate cellular enzymes (for example, those used to repair radiation damage), and high level heating can damage blood vessels.[7-13] While all tissues are primarily cooled by blood flow, neoplastic tissues are particularly heat sensitive. This is thought to be because they have poorly developed vascular systems which are often redundant and inefficient, leading to poor perfusion, necrosis, acidosis, and hypoxia.[14-18] When heat is delivered to a cancer, the poorly perfused (radiation resistant) areas concentrate heat and are preferentially damaged.[17 18]

For effective clinical hyperthermia it is necessary that heat delivery systems be tailored to account for the blood flow and location of the tumour. Ideal heat distributions target the neoplasm and/or its vascular supply with relative sparing of normal tissues. Choroidal melanomas seem uniquely vulnerable to microwave thermotherapy. These are comparatively small tumours which project into the avascular vitreous and are therefore largely dependent on basal blood vessels emanating from the choroid. Episcleral application of a microwave plaque targets the base of an intraocular tumour and preferentially heats its vascular supply.[19-21] The only normal structures to receive high dose thermotherapy are the relatively heat resistant sclera and cornea directly beneath the episcleral plaque.[22 23]

In this series microwave thermotherapy was used in conjunction with plaque radiotherapy for treatment of 44 patients with choroidal melanoma. Encouraged by early reductions of tumour height, we reduced the minimum tumour radiation dose (tumour apex) to levels used in treatment of cutaneous melanomas.[1-3] The associated reductions in radiation to normal ocular structures should decrease the incidence of radiation-associated complications.

This report includes a description of microwave plaque construction, the technique of treatment, microwave and radiation dosimetry, and clinical observations.

Materials and methods

All patients in this series were diagnosed as having choroidal melanoma by clinical examination. Since the time we joined the Collaborative Ocular Melanoma Study (COMS) all eligible patients were told of two standard methods of treatment available to them through participation in the COMS.[24] Ineligible patients and those who refused to join the study were offered observation, enucleation, radiation, or radiation with microwave hyperthermia. This involved a detailed discussion of the risks and benefits of each therapeutic form as it related to their tumour's size, location, and risk of metastasis.

Hospital Internal Review Board (IRB) approvals and a United States of America, Food and Drug Administration investigational device exemption (IDE) were obtained prior to this clinical study. All patients were informed of the investigative nature of microwave thermotherapy. They were told of how many patients had been treated, how long they had been followed-up for complications or recurrence, and the significance of those facts. The mechanism of action of adjuvant heat therapy in other tumour systems, and the rationale for reducing the amount of ionising radiation delivered to the tumour's apex were also explained as well as possible.[1-3] Though no significant scleral damage has been noted in this series, the possibility of such damage (as noted in preclinical studies) was discussed.[20]

The patients had a complete eye examination prior to treatment. After refraction, pupillary, ocular motor, and slit-lamp examinations were performed. Goldmann tonometry was used to measure intraocular pressure. Ophthalmoscopy was performed with direct, indirect and contact lens techniques as applicable. Standardised echography was performed.[25] A-scan was used to measure tumour height and evaluate internal

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Accepted for publication
21 November 1991

reflectivity. B-scan echography was used to determine tumour location, shape, associated retinal detachments, and to evaluate choroidal excavation or extrascleral tumour extension. Fluorescein angiography, slit-lamp, and fundus photography were performed when possible.

All tumours in this series had base diameters greater than 10 mm or heights greater than or equal to 3 mm. Six patients had large melanomas as defined by a tumour height greater than 8 mm, and 38 had medium sized tumours with heights greater than or equal to 3 mm. No patients with a tumour basal diameter of greater than 16 mm were treated. Three patients had ciliary body melanomas, and three juxtapapillary tumours were contiguous with the optic nerve (Table 1).

Preoperative investigations for metastases were performed on all patients. They included a physical examination, blood tests (sequential multiple analyser profile (SMA-12), gamma-glutamyl transpeptidase (GGT), complete blood count (CBC)), and a chest *x* ray. Computed axial tomography of the orbits was performed if extraocular extension was suspected on ultrasonography. Computed tomography of the abdomen was performed for increased liver enzymes or at the patient's request.

In most cases the patients were examined after surgery, at 24 hours, 7 days, 1 month, 3 months, then every 3 months for 2 years, and finally at 6-month intervals. Examinations included tests of visual acuity, pupillary function, ocular motor function, a slit-lamp examination, intraocular pressure measurements, and ophthalmoscopy. Ultrasonography, fundus photography, and fluorescein angiography were also used to evaluate tumour response and ocular health. Systemic examinations were performed approximately each year after treatment. These included a physical examination, repeat haematological studies, and chest *x* ray.

MICROWAVE THERMOTHERAPY

Plaque construction

Microwave plaques were constructed by MMTC Corp (Princeton, NJ, USA), and thermocouple assemblies were added at Brookhaven National Laboratory (Upton, NY, USA). The resonant portion of the disc-shaped antenna was constructed by photoetching a copper disc on the surface of a Teflon fibreglass dielectric substrate (RT-Duroid 5880, Rogers Corp, Chandler, AZ, USA). The etching process selectively left a 2 mm free margin between the copper disc and the edge of the antenna (Fig 1).[20 24]

A short length of flexible silicone-covered coaxial cable AS 450–3650 SR (Cooner Wire, Chatsworth, CA, USA) was used to direct the microwave energy from the microwave generator/amplifier to the patch antenna. The silicone coating was removed at one end which exposed the centre conductor. To form an electrical return, the outer mesh was soldered to the copper backing of the duroid substrate. Then the

Table 1 Patient data: tumour size, location, and shape

Number	*Surgery*	*Length*	*Width*	*Height*	*Eye*	*Clock h*	*Apex Loc.*	*mm to ON*	*mm to F*	*Shape*
1	Jul-86	15	15	3	Right	3:00	EP	3·4	0	Dome
2	Aug-86	7	10	3	Right	6:00	EA	7	8	Dome
3	Oct-86	9	7	3·5	Left	8:00	EP	8	11	Dome
4	Jan-87	16	16	12·2	Right	4:00	E	7	10·4	Collar B
5	Mar-87	12	8	4	Left	5:30	E	6·2	6	Dome
6	May-87	15	15	10	Right	10:00	E	10	13·4	Collar B
7	Jun-87	8	6	3	Right	7:30	EA	16	15·6	Dome
8	Jul-87	6	5	4·7	Left	1:30	PE	1·5	1·5	Collar B
9	Aug-87	8	8	3·7	Left	4:30	PE	3	4·5	Dome
10	Oct-87	14	12	8·4	Left	4:00	E	10	12	Collar B
11	Oct-87	15	14	4·4	Left	3:00	EA	14	10·6	Dome
12	Nov-87	10	8	3·9	Left	5:00	EP	6	5	Dome
13	Feb-88	12	12	5·7	Right	6:30	PE	1	1·5	Dome
14	Apr-88	10	8	3·7	Left	10:00	EA	11·7	12·2	Dome
15	Sep-88	8	8	3·2	Left	9:00	E	4	7	Dome
16	Nov-88	15	15	3·4	Left	7:30	EP	2	7·5	Dome
17	Dec-88	7·5	5·5	3·4	Right	10:30	EP	7·5	5	Dome
18	Jan-89	14	12	3·9	Right	9:30	E	11	7·5	Dome
19	Feb-89	11	11	6·4	Right	12:30	P	0	0	Collar B
20	Apr-89	15	12	5·7	Left	2:30	PE	3	0	Dome
21	Jun-89	12	12	7·4	Right	8:00	EP	3·5	1	Dome
22	Jul-89	9	9	3·7	Left	3:30	E	10	6	Dome
23	Jul-89	9	8	8·1	Right	4:30	E	4	7·5	Collar B
24	Jul-89	10	8	5·2	Left	3:30	E	7	3·5	Dome
25	Sep-89	8	6	3·2	Left	5:00	P	0	0	Dome
26	Oct-89	10	10	5·2	Left	10:00	P	1·5	4·5	Dome
27	Nov-89	6	5	3·2	Left	3:00	PE	1·5	0	Collar B
28	Nov-89	10	10	5·4	Right	3:00	CB	17	19·3	Dome
29	Nov-89	10	10	3·2	Right	8:00	P	0	0	Dome
30	Jan-90	8	6	5·9	Left	4:00	PE	1	0	Dome
31	Feb-90	10	9	5·2	Left	8:00	CB	17·3	19·6	Dome
32	Feb-90	10	10	6·4	Left	2:00	PE	3	1·5	Dome
33	Feb-90	10	9	3·7	Right	3:30	E	7·5	10·5	Dome
34	Mar-90	10	10	6·6	Right	10:00	PE	5	2	Collar B
35	May-90	9	7	4·7	Right	8:00	P	1·5	0	Dome
36	Jun-90	11	10	8·1	Right	5:00	EP	1·5	1·5	Collar B
37	Jun-90	7	7	3·4	Left	7:00	CB	17	19·5	Dome
38	Jul-90	9	7	3·2	Left	2:00	EP	5·4	2	Dome
39	Aug-90	12	12	5·9	Right	3:00	EA	7	10·4	Dome
40	Sept-90	10	10	3·4	Right	8:00	EP	12	8	Dome
41	Sep-90	16	16	5·9	Left	3:30	EP	3·4	0	Dome
42	Sep-90	10	10	4·2	Left	2:00	EP	3·5	1	Dome
43	Oct-90	12	10	8·6	Right	9:00	E	11	7·4	Collar B
44	Feb-91	10	10	3·4	Right	10:00	EP	5	1·5	Dome

Ultrasonic apex locations: P=posterior; PE=posterior equator; EP=equator posterior; E=equator; EA=equator anterior; CB=ciliary body.

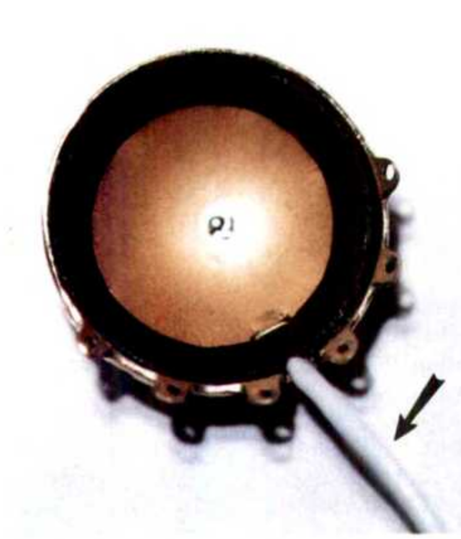

Figure 1 A plaque-shaped microwave antenna affixed within a gold episcleral plaque, a white miniature coaxial cable is noted leaving the plaque (arrow). The plaque is shown prior to thermocouple assembly and silicone insulation for better visualisation.

exposed centre conductor was placed through a central hole drilled in the disc-shaped antenna and soldered on to its anterior surface. Lastly a U-shaped wire was inserted through holes at the edge of the copper etched surface and soldered on the top and bottom surfaces to complete the circuit.

To monitor temperatures during treatment three copper-constantan thermocouples were affixed (cyanoacrylate to the anterior surface of the microwave antenna and bent 90° to bring the thermocouple tips into contact with the sclera. The anterior surface of the microwave dish was insulated up to the tips of the thermocouples with silicone adhesive (Dow Corning Corp, Midland, MI, USA). Though temperatures were constantly monitored within the microwave field by means of an optically isolated computer controlled TM-12 thermometry system (Physitemp, Clifton, NJ, USA), after patient 10 the treatment temperatures were determined when the field had been turned off for 2 seconds. This was called microwave 'field-off' technique. This technique minimised the effect of the microwave field on the metallic thermocouples and thereby reduced the possibility of temperature artefact.

Table 2 Methods

Number	*Base dose (Gy)*	*6 mm dose (Gy)*	*Apex dose (Gy)*	*Apex dose (rate cGy/h)*	*Temp (°C)*	*Time (minutes)*	*F/U (months)*
1	195	59	88	68	47	45	12
2	200	54	85	113	47	45	52
3	211	62	88	125	48	45	48
4	454	141	40	40	50	45	55
5	219	66	80	110	50	45	48
6	535	156	66	40	52·5	45	29
7	124	37	58	110	52	45	21
8	302	70	79	85	50	45	36
9	236	45	63	118	52	45	44
10	263	89	59	58	49	45	46
11	193	59	68	98	49·3	45	42
12	132	41	52	120	47·1	45	11
13	221	67	60	89	46·9	45	34
14	143	44	59	80	47·3	45	36
15	204	43	64	95	50·1	45	31
16	111	39	50	90	48·7	45	32
17	162	34	50	140	49·4	45	26
18	130	45	53	57	49·7	45	11
19	228	66	50	68	49·5	45	19
20	164	57	49	60	48	45	21
21	262	81	52	80	49·5	45	24
22	175	41	56	48	50·5	45	12
23	378	95	51	37	50	45	24
24	228	57	55	78	49·7	45	24
25	148	30	48	93	47·3	45	18
26	215	56	52	73	49·5	45	18
27	176	27	45	58	48	45	18
28	200	50	48	100	48·4	45	18
29	153	39	60	88	47·6	45	8
30	257	60	50	69	46·6	45	12
31	201	47	45	62	47·4	45	15
32	292	73	55	76	47·3	45	18
33	165	42	56	116	47	45	16
34	296	74	53	74	49·5	45	12
35	206	52	55	70	48	45	10
36	290	91	50	67	47·4	45	12
37	151	34	50	70	47·5	45	12
38	124	31	48	67	47·6	45	12
39	193	60	50	70	47·9	45	12
40	106	26	39	54	47	45	9
41	150	52	43	45	48·2	45	8
42	158	39	48	89	48	45	11
43	290	94	46	61	49	45	9
44	136	33	50	70	47	45	6

Microwave treatment

All patients in this series received one microwave thermotherapy treatment. Surgical implantation of the episcleral radioactive plaques was performed by standard and ring transillumination tumour localised techniques.[27] Small, posteriorly located tumours were often localised by scleral depression. During transillumination the edges of the tumour were marked on the sclera with tissue dye. Then a hand held cautery was used to mark episclera. These marks were used for placement of the microwave antenna at the time of radioactive plaque removal. Microwave applicators were chosen such that the diameter of the copper portion of the antenna would equal or (more commonly) exceed the tumour's basal diameter by 1–2 mm. The active surface of the microwave antenna was pressed against the sclera beaneath the choroidal tumour. Unlike radioactive plaque therapy, microwave thermotherapy required firm contact between the active surface of the plaque and the sclera. Thermotherapy was performed for 45 minutes. The first 10 patients were treated as high as 52·2°C (as measured within the microwave field). Since that time all patients were treated to 'field-off' episcleral temperatures in a range of 47–50°C (Table 2). Since we know that our microwave applicators lose on average 1°C per axial millimetre into the eye and/or tumour, episcleral temperatures were selected so as to target the tumour's apex to a minimum of 42°C. This assumption was based on experiments performed with our applicators in rabbit eyes and phantom materials.[19–21 28] Similar intraocular heat distributions have been reported by Reidel *et al*[29] and Swift *et al*[30] using equivalent or ring-type microwave applicators.

RADIATION TREATMENT

Standard COMS-type gold plaques (Trachsel Dental Studio Inc, Rochester, MN, USA) were used in most cases. Radioactive I-125 seeds were available (3M Corp, St Paul, MN, USA) at strengths ranging from 0·5 to 40 mCi/seed, and palladium-103 seeds were available (Theragenics Corp, Norcross, GA, USA) at strengths of up to 2 mCi/seed. Each seed's strength was checked in a well counter prior to plaque assembly.

Dosimetric calculations were performed in a manner similar to the COMS protocol, in which a number of assumptions were required. All the seeds were calculated as point sources (no correction for anisotrophy). No attenuation effect was attributed to the side walls of the gold plaque, the silastic seed carrier, or acrylic used to hold the seeds within the plaque.[31] The radiation enhancing effect of 'back scatter' from the posterior wall of the gold plaque was discounted.[32] Lastly, the US National Cancer Institute (NCI) Brachytherapy Contract Group suggests that the dose rate constant for I-125 may be up to 19% lower than their measured values.[33] To make our findings comparable with the results from our experience and the clinical standard at most centres, this study incorporates the same approximate dose inflation factor of 19%. Our calculations used the specific dose rate constants of (1·32 cGy/h/mCi) for I-125 and (1·09 cGy/h/mCi) for Pd-103, which were standardised at 1 cm in water.[34-39]

All patients in this series received one radiotherapy treatment. Radioactive plaque (I-125, Pd-103) brachytherapy started at insertion and continued until the prescribed dose was delivered to the tumour's apex (Table 2). Though 44 patients with choroidal melanoma have been treated, there are three treatment groups.

The first group of 10 patients were treated with I-125 plaque radiation and microwave thermotherapy (during or after radiotherapy). Temperatures were measured within the microwave field and are therefore not comparable to subsequent patients' thermal doses. Their mean apex radiation dose (minimum tumour dose) was 65 Gy, and their mean follow-up has been 39 months (Table 2).

The second group, the largest and the most notable set of 29 patients, were treated with a combination of I-125 plaque radiotherapy followed by microwave thermotherapy. Temperatures were determined with 'field-off' technique. Their mean apex radiation dose was 53 Gy, and their mean follow-up has been 19 months (Table 2). A relatively uniform method and thermoradiotherapy dose were used for this group.

The third group of patients (five patients) were treated with the same relatively uniform thermoradiotherapy method and dose as group 2, except that Pd-103 seeds were used instead of I-125 for plaque radiotherapy. Thermotherapy temperatures were determined by 'field-off' technique. The mean apex radiation dose was 45 Gy, and their mean follow-up has been 9 months (Table 2). Though the type of radiation emitted from Pd-103 seeds was the same as from I-125 owing to greater absorption in tissue the normal ocular structures were calculated to receive significantly less radiation with Pd-103 than with I-125.[39-41]

Results

We report on the first clinical trial of microwave thermotherapy for the treatment of choroidal melanoma. This was a non-randomised phase-I clinical trial, from which evolved a technique for adjuvant microwave thermotherapy for treatment of intraocular tumours. In that most heat-related side effects are likely to occur during or immediately after treatment, all microwave treated eyes (treatment groups) were significant.

There have been three side effects which could be attributed to microwave thermotherapy. The first and most important has been chorioretinal attenuation within and anterior to the treatment zone (Fig 2). No evidence of scleral damage has been noted on either ophthalmoscopy or ultrasonography. This reaction has been noted in a total of 13 patients (12 of whom were treated with 'field-off' technique). The second side effect may be related to this chorioretinal reaction. Eyes with tumours anterior to the equator or involving the ciliary body were noted to have persistently decreased intraocular pressure (without hypotony). The third side effect was a relatively non-progressive anterior subcapsular cataract noted in patient 17 immediately after surgery (Table 3A).

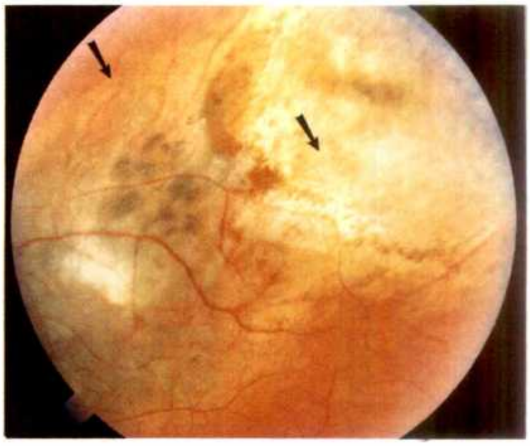

Figure 2 An area of chorioretinal attenuation is noted around and anterior to the tumour's base in a patient 10 months after being treated with 55 Gy (apex) 48°C × 45 min thermoradiotherapy (arrows).

In 44 patients there has been one possible failure of local control (defined as documented tumour growth greater than 15% in apical height). Patient 32's tumour was 10×10×6·4; after 18 months his tumour has grown to 7·4 mm, while its basal dimension has remained unchanged. This tumour was treated to a basal radiation dose of 292 Gy, an apical radiation dose of 55 Gy, and is being followed-up for further documentation of growth.

There have been two enucleations, one in patient 10 for glaucomatous complications of a bilateral uveitis 39 months after treatment, the second in patient 19 for rubeotic glaucoma 19 months after treatment. Ten patients have developed some form of secondary retinopathy (Table 3B). Three had pre-existing diabetes and developed an asymmetric diabetic like non-proliferative retinopathy. Patient 19 had a total exudative 'tumour-dissolution' retinopathy[42] leading to the rubeotic glaucoma, and two have developed radiation retinopathy (one with an associated optic neuropathy). Two have developed rings of exudate round their tumours, and two have developed subretinal neovascularisation within the treatment zone. Argon laser photocoagulation has been used to treat the two cases of subretinal neovascularisation (SRN), and panretinal photocoagulation has been used in the one case of radiation retinopathy with optic neuropathy. There have been two cases of perioperative subretinal tumour haemorrhage (Table 3B). Both occurred in patients with pre-existing diabetes, and in one (patient 18) blood dissected to the macula and caused persistent decreased vision (Table 4).

Patterns of visual acuity change were largely dependent on pre-existing ocular conditions: the proximity of the tumour to the fovea, the presence of retinal (foveal) detachment, vitreous haemorrhage, cataract, and cystoid macular oedema. Postoperative patterns were largely dependent on the resolution of foveal detachments, vitreous haemorrhages, the development of cataract (radiation and non-radiation induced), the appearance of radiation maculopathy, and/or cystoid macular oedema. At this follow-up interval 13 patients have lost two or more lines of vision (including the two patients whose eyes were enucleated). Among the 11 remaining patients who experienced serious visual loss, the condition in two was primarily caused by persistent retinal detachments through their foveas, in two it was due to treatment-associated cataract formation, in two due to natural progression of pre-existing cataracts, in two due to increased diabetic retinopathy, in one to perioperative subretinal haemorrhages with secondary macular damage, in one to an exacerbation of a pre-existent cystoid macular oedema, and in one to internal limiting membrane wrinkling through his fovea. Five patients are currently experiencing improvement of two or more lines in visual acuity. Four were secondary to resolved foveal detachments, and one has been due to resolution of his cystoid macular oedema (Table 4).

Table 3A Anterior segment morbidity

Number	*Lash loss*	*Keratitis*	*Sicca*	*Rubeosis*	*Glaucoma*	*Cataract*
1						
2						Post-tx
3						
4						Post-tx
5						
6						Pre-tx
7						
8						
9		Pre-tx	Pre-tx		Pre-tx	Pre-tx
10					Uveitic	Uveitic
11						Post-tx
12						
13						Pre-tx
14						
15						
16						
17						Post-tx
18						Post-tx
19				Post-tx		
20						
21						
22						
23						Pre-tx
24						
25						
26						
27						
28						Post-tx
29						
30						
31						Post-tx
32						
33						
34						Post-tx
35						
36						
37						Pre-tx
38						
39						
40						
41						
42					Pre-tx	
43						
44						

Pre-tx=pretreatment; post-tx=post-treatment.

Table 3B Posterior segment morbidity

Patient no	*Chor-ret damage*	*Retinal detachment*	*Retinopathy*	*Retinopathy type*	*Vitreous haem*	*Subretinal haem*	*Cystoid macular oedema*	*Nerve damage*
1		Pre-tx						
2								
3								
4	Yes							
5					Pre-tx		Pre-tx	
6		Pre-tx			Pre-tx			
7								
8		Pre-tx	Post-tx	Radiation				
9					Pre-tx			
10								
11		Post-tx		Pre-tx				
12			Post-tx	Incr BDR				
13								
14								
15	Yes							
16	Yes	Pre-tx						
17								
18		Operative				Operative		
19			Post-tx	Total exud				
20								
21		Pre-tx	Post-tx	ILM, fovea				
22								
23			Post-tx	SRN				
24								
25								
26	Yes		Post-tx	Radiation			Post-tx	
27			Post-tx	SRN				
28	Yes							
29	Yes							
30		Pre-tx	Post-tx	Exud ring				
31	Yes							
32		Pre-tx						Pre-tx
33								
34	Yes	Pre-tx						
35	Yes							
36			Post-tx	Exud ring	Post-tx		Post-tx	
37	Yes	Operative				Operative		
38								
39	Yes	Pre-tx	Post-tx	Radiation				Post-tx
40								
41								
42	Yes		Post-tx	Incr BDR				
43								
44	Yes							

Pre-tx=pretreatment; post-tx=post-treatment; BDR=background diabetic retinopathy; SRN=subretinal neovascularisation; ILM=internal limiting membrane.

Table 4 Results

Number	*Apex height pre-tx*	*Apex height most recent*	*Vision pre-tx*	*Vision most recent*	*Vision change primary cause*	*F/U months*	*Death*
1	3	2·9	20/40	20/25	Decr SRF	12	MI
2	3	0·9	20/25	20/30		52	
3	3·5	1·4	20/20	20/15		48	
4	12·2	8·4	20/200	20/200		55	
5	4	1·9	20/200	20/50	CME/Vitr haem	48	
6	10	7·6	HM	FC		29	MI
7	3	1·8	20/60	20/60		21	MI
8	4·7	2·9	20/200	20/200		36	
9	3·7	1·7	20/200	20/200		44	
10	8·4	4·7	20/40	NLP	Enucleation	46	
11	4·4	1·2	HM	HM		42	
12	3·9	2·7	20/20	20/40	Incr BDR	11	Sepsis
13	5·7	0·9	HM	LP		34	
14	3·7	1·7	20/30	20/20	Unknown	36*	Melanoma
15	3·2	1·2	20/25	20/30		31	
16	3·4	2·2	20/50	20/25	Decr SRF	32	
17	3·4	2·2	20/15	20/30	Heat cataract	26	
18	3·9	1·4	20/25	20/200	Sub ret haem	11	
19	6·4	5·4	20/200	NLP	Enucleation	19	
20	5·7	2·7	20/30	20/40		21	
21	7·4	6·2	20/20	20/30	ILM foveopathy	24	
22	3·7	2·9	20/20	20/20		12	
23	8·1	7·4	20/40	20/60	Non-RT cataract	24	
24	5·2	1·2	20/40	20/50		24	
25	3·2	2·2	20/200	20/200		18	
26	5·2	5·2	20/40	20/30		18	
27	3·2	1·4	FC	FC		18	
28	5·4	2·4	20/25	20/20		18	
29	3·2	2·7	20/400	FC		8	Cancer
30	5·9	4·4	20/70	20/200	PSRF	12	
31	5·2	1·2	20/30	20/30		15	
32	6·4	7·4	20/40	FC	PSRF	18	
33	3·7	2·2	20/20	20/20		18	
34	6·6	4·4	20/60	FC	RT Cat. PSRF	12	
35	4·7	3·9	FC	20/400		10	
36	8·1	5·7	20/30	FC	CME	12	
37	3·4	2·2	20/40	20/50		12	
38	3·2	2·4	20/30	20/50	Non RT Cataract	12	
39	5·9	4·4	20/400	20/30	Decr SRF	12	
40	3·4	2·9	20/20	20/25		9	
41	5·9	5·2	20/100	20/40	Decr SRF	8	
42	4·2	4·2	20/30	20/200	Incr BDR	11	
43	8·6	5·9	20/40	20/40		9	
44	3·4	2·2	20/20	20/20		6	

*Metastasis; CME=cystoid macular oedema; MI=myocardial infarction; PSRF=persistent subretinal fluid; RT=radiation therapy; SRF=subretinal fluid.

As measured by ultrasonography, microwave thermoradiotherapy caused a greater than 0·3 mm reduction in apical tumour height in 40 patients, less than a 0·3 mm decrease or no change in three patients. An increased apical tumour height (greater than 15% increase in tumour height) in one patient for a 97·7% local control rate (Table 4).

Six patients have died: three of heart disease, one of sepsis, one of metastatic prostate cancer, and one patient of metastatic choroidal melanoma (39 months after treatment) (Table 4).

Discussion

In the treatment of choroidal melanoma radiotherapy has been used to stop tumour growth or achieve shrinkage in over 90% of cases.[41 43-49] After treatment 30 to 40% of eyes have experienced significant radiation-associated ocular complications.[49-55] The incidence and location of complications were related to the method of radiation delivery, the size of the tumour (therefore the amount of radiation delivered to the eye), the location of the tumour, and its response to radiotherapy.

In plaque treatment a radioactive device was sutured to the sclera beneath the intraocular tumour. Radiation then travelled through and was absorbed by the eye wall, the tumour, the vitreous, and by normal ocular structures. To decrease radiation-associated complications one must lower the dose to normal ocular structures without compromising local tumour control. We have used an adjuvant therapy, namely microwave thermotherapy, to reduce the minimum tumour dose (apex dose) to levels used for thermoradiotherapy of cutaneous melanomas. By reducing the amount of radiation delivered to the tumour apex to approximately 50 Gy (5000 rad tumour apex dose) the amount of radiation delivered to normal ocular structures has been decreased by 50% or more in comparison with most centres.[24]

Because hyperthermia has been shown to make radiation therapy more effective, a number of methods to produce hyperthermic treatment of intraocular tumours are being investigated.[19-21 26 30 56-63] A comparison of the physics and energy deposition characteristic of each heat delivery system as it relates to ocular hyperthermia is not within the scope of this paper. Microwave heat delivery systems appear to be the most commonly used forms of hyperthermic treatment of cancer.[64] This is because microwave cables are easily incorporated into implanted brachytherapy catheters, and deep tissue heating can be induced with surface applicators. The antennas described in this series were both implanted and required to induce heat at depth from the sclera.

In a non-randomised phase I clinical trial the ophthalmic microwave plaques described were employed to deliver adjuvant thermotherapy to 44 choroidal melanomas. The results of this study indicate that microwave plaque thermotherapy can be performed as an adjuvant to radiotherapy of choroidal melanoma. In comparison with published reports on complications after radiotherapy of choroidal melanoma there have been no new complications which might preclude the use of this system of adjuvant microwave plaque thermotherapy.[49-55]

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British Journal of Ophthalmology, 1992, 76, 365–366

MINI REVIEW

Herpes simplex virus in the eye

The herpes simplex virus (HSV) remains a significant ocular pathogen despite the existence of highly specific antiviral agents. The clinical spectrum of recrudescent ocular disease induced by HSV involves predominantly the anterior segment and includes HSV shedding in the tear film in the absence of disease; dendritic ulcers (epithelial disease); stromal keratitis with overlying epithelial disease; and stromal keratitis with underlying endothelial disease (disciform keratitis). In addition HSV has been implicated in scleritis and uveitis. HSV is also one of many viruses which have been linked to multiple sclerosis. It is postulated that the viruses have a shared epitope with myelin binding protein.

HSV and varicella zoster virus are the pathogens most commonly detected in the acute retinal necrosis syndrome (ARN). Some similarities exist between ARN and the retinitis induced by cytomegalovirus (another member of the herpes group) in AIDS patients. ARN has also been described in AIDS patients. ARN was reviewed recently by Duker and Blumenkrantz.[1]

It is uncommon for ophthalmologists to see primary HSV disease which may be manifest as a follicular conjunctivitis. Suspicion of a primary HSV infection is confirmed by rising titres of antibodies to HSV. Primary and recrudescent HSV infections can be treated successfully by antiviral agents, the most specific of which is acyclovir. Despite the widespread use of antiviral agents it is extremely rare for clinical isolates of HSV to exhibit resistance.[2]

In anterior segment disease delay in treatment, frequent recurrences, and mistreatment can all result in visual impairment. It is the author's clinical impression that mistreatment with steroids by primary care physicians is becoming increasingly rare. The immunological response to HSV is generally protective for the body. However in the localised context of the cornea an immunological response is often detrimental to its function leading to scarring. The complex response to HSV involving many arms of the immune system has been comprehensively reviewed by Pepose.[3] Corticosteroids may lead to an increased duration of herpetic disease by interrupting the immune system but it is unlikely that they induce viral reactivation. A prolonged corneal infection may be a factor in the genesis of possible latent infections within the cornea. Since the first report of HSV being isolated from human corneas with herpes simplex keratitis after organ culture,[4] evidence has accumulated from human and animal studies suggesting that the cornea may be capable of harbouring latent HSV infections (reviewed by Cook and Hill[5]). If a latent infection can be maintained in a non-neuronal site, then reactivation from a latently infected cornea is likely to be clinically indistinguishable from HSV reactivation in a neuronal site with a subsequent corneal recrudescence. HSV DNA sequences have been detected in a small number of human corneas with no past history of herpetic eye disease.[6,7]

These HSV sequences may be only fragments of DNA incapable of reactivation, but the presence of HSV DNA in 'normal' corneas has important implications for transplantation. Tullo *et al*[8] described the isolation of HSV in the organ culture medium of a corneoscleral disc from a corneal donor. One further HSV isolate has been obtained from another corneal donor in the same laboratory (A B Tullo, personal communication). Neither cornea was used in transplantation.

Reduced visual acuity as a consequence of herpes simplex keratitis remains one of the commonest indications for corneal transplantation in the UK. Between 1987 and 1991 10·5% of 3200 transplants supplied through UKTSSA were performed because of herpes simplex keratitis (A Vail, UKTSSA, personal communication). A study from the Moorfields Corneal Clinic suggests that the expected long term survival for first transplants in quiescent corneas with herpes simplex keratitis is 70%.[9] Earlier studies from the same clinic reported 45% long term survival.[10,11] The improvement in graft survival was aided by prompt removal of loose sutures, concurrent antiviral treatment with immunosuppression during rejection episodes, and prompt treatment of recrudescent HSV disease.

Although the HSV genome has been completely sequenced and is known to contain 70 genes, many of the genes are uncharacterised by structure or function. Different HSV strains show varying degrees of neurovirulence, corneal disease, and reactivation frequency. Specifically engineered HSV mutants with defects in isolated genes are providing valuable information in the biological functions of HSV in laboratory and animal studies. However the greatest enigma in the study of HSV remains the relationship between the virus and the host cell during latency and reactivation, reviewed by Garcia-Blanco and Cullen.[12]

In the HSV lytic cycle the virion carries a protein in its tegument that transactivates its own immediate early genes. This initiates sequential expression of immediate early, early, and late genes culminating in the production of new HSV virions and the destruction of the host cell. The tegument protein mediates this transactivation in association with two cellular factors.[13] Studies suggest that the tegument protein is non-functional in neural cells.[14] This may be because a cellular factor is lacking in neurons,[15] or because neurons express a protein inhibiting the function of the tegument protein.[16] The result may be that the lytic cycle aborts and a latent infection is established.

During latency infectious HSV is undetectable within the host cell. The only detectable mRNAs are the latency associated transcripts (LATs) first described by Stevens *et al.*[17] No protein encoded by LATs has been detected in vivo, although an antigen encoded by LATs has been detected in latently infected neuronal cell cultures.[18] LATs are not essential for the establishment and maintenance of latency.[19–21]

Clinicians are familiar with the concept of trigger factors for HSV reactivation. Many diverse stimuli can induce reactivation and a final common pathway is likely. LATs may play a role in reactivation. LAT mutants have been shown to reactivate less efficiently in vivo.[21] The downstream end of the LAT gene overlaps with the downstream end of an immediate early gene, ICP0. The two genes run in opposite orientations. ICP0 is an important regulatory gene; it transactivates itself; it regulates early and late gene expression and it is important in reactivation.

Although education, specific antiviral agents, and refinements in surgical technique have improved the prognosis for patients with herpes simplex keratitis the condition persists. More than 80% of the community have antibodies against herpes simplex virus. Current treatment options are only effective in eliminating replicating virus or suppressing an immune response to viral antigens. As yet no therapy has been devised to block reactivation. Such a therapy may also be impractical for prophylaxis given the often long intervals between recurrent episodes of disease. Vaccination may yet be the answer to the prevention of primary HSV infections with subsequent recrudescent disease, but given that HSV has devised the strategy of latency to avoid the immune system, developing an appropriate vaccine represents a considerable challenge.

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British Journal of Ophthalmology, 1992, 76, 367–368

CASE REPORTS

Treatment failure in a case of fungal keratitis caused by *Pseudallescheria boydii*

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Abstract

A case is presented of *Pseudallescheria boydii* fungal keratitis in an agricultural welder. Treatment with azole antifungal drugs (miconazole and itraconazole) and with penetrating keratoplasty was unsuccessful in eradicating the infection, and eventually the eye was eviscerated.

Case report

A 57-year-old man presented with a painful red eye. Ten days previously he had been welding in a pig slurry tank while wearing a face mask, but recalled no injury. An ulcer noted on the right cornea initially was thought to be herpetic and treated with 3% acyclovir ointment. Three days later 0·1% dexamethasone drops four times a day were added. One week later the ulcer had greatly extended and topical steroids were stopped.

Microscopy following extensive lamellar corneal debridement (biopsy) showed massive fungal infection. The organism was later identified as *Pseudallescheria boydii*, but sensitivity tests were not performed on this isolate. Treatment was instituted with 1% miconazole drops hourly and itraconazole 200 mg once a day orally, and a subconjunctival injection of miconazole 0·5 ml of 10 mg/ml was given. The ulcer did not improve, so 1 week later further corneal debridement was performed and the subconjunctival miconazole was repeated. Systemic antifungal treatment was changed to miconazole 600 mg three times a day intravenously, but the ulcer continued to enlarge. Ten days later the patient was transferred to Bristol Eye Hospital.

On admission the cornea was hazy and thickened with a deep central ulcer and marked stromal infiltrate (Fig 1). The anterior chamber was deep with an intense fibrinous exudate and a 2·5 mm hypopyon. Following deterioration, an 8 mm eccentric right penetrating keratoplasty and clearout of the anterior chamber exudate were performed 3 days after transfer (5 weeks after presentation). *Pseudallescheria boydii* was isolated from excised cornea and anterior chamber fibrin, but there was no bacterial growth from these specimens. Microscopy showed fungus up to the corneal resection margin.

Because of the patient's clinical deterioration before surgery, postoperative antifungal treatment was changed from miconazole to itraconazole, initially 200 mg once a day orally. Topical 1% miconazole was continued.

Twelve hours postoperatively there was a marked fibrinous anterior uveitis and the donor corneal button was thickened and hazy. Over the next 2 days the graft cleared but the hypopyon reformed, so 0·1% dexamethasone drops four times a day were added. The fibrinous reaction progressed with lifting of the graft, and the dexamethasone was increased to 2 hourly. This failed to halt the progression to endophthalmitis (Fig 2).

Serum concentrations of itraconazole were low (0·2 mg/l at 4·5 hours), so the dose was increased to 200 mg twice a day. The results of sensitivity testing of the Bristol corneal isolate became available 4 days postoperatively. These showed that the organism was sensitive to miconazole (minimum inhibitory concentration [MIC]= 0·5 mg/l), but resistant to amphotericin B (MIC=5 mg/l) and itraconazole (MIC >50 mg/l). Miconazole 600 mg intravenously three times a day was therefore recommenced. This was later increased to 1200 mg three times daily in combination with hourly topical miconazole 1% and two further subconjunctival injections of miconazole.

The endophthalmitis did not respond, however, and the patient became depressed and nauseated from systemic treatment. Because clinical success was deemed unlikely, the patient requested evisceration, which was performed 8 weeks after the original infection. *Pseudallescheria boydii* was isolated from evisceration specimens of cornea and anterior chamber fibrin but not from lens or vitreous.

Discussion

Fungal keratitis is most prevalent in agricultural workers in the rural populations of tropical areas, following traumatic implantation of fungal spores from soil or plant matter into the corneal stroma.

Pseudallescheria boydii (previously *Petriellidium boydii, Allescheria boydii, Monosporium apiospermum*) is a ubiquitous fungus that has been isolated from soil, polluted water, and sewage. It has been reported to cause keratitis, endophthalmitis, mycetoma, pneumonia, osteomyelitis, arthritis, sinusitis, endocarditis, meningitis, and brain abscess.[1] In immunosuppressed patients infection may result in fatal disseminated pseudallescherosis.

There have been at least 14 reported cases of *P boydii* keratitis[2] but none treated with itraconazole, a recently introduced orally adminis-

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Accepted for publication
14 November 1991

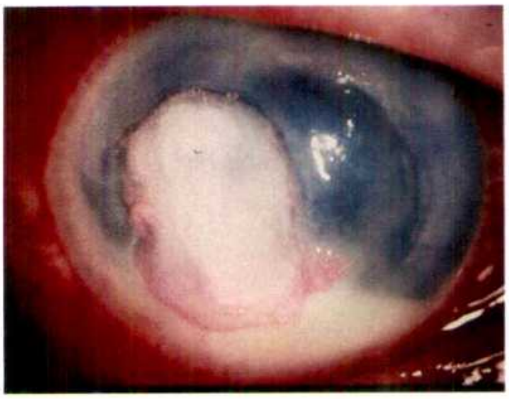

Figure 1 Corneal ulcer with hypopyon, due to Pseudallescheria boydii.

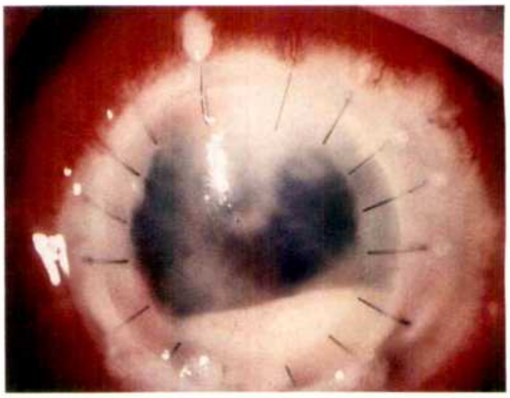

Figure 2 Reformed hypopyon after penetrating keratoplasty for Pseudallescheria boydii *keratitis. A stitch abscess can be seen superiorly.*

tered broad-spectrum triazole compound. In only five of these 14 cases was treatment successful, the remainder requiring evisceration. Although many isolates of *P boydii* are resistant to amphotericin B,[3] several cases of keratitis have been successfully treated with this drug alone, or in combination with nystatin or natamycin.[4-6]

Although many strains of *P boydii* are sensitive to miconazole,[3 7] there have been no published reports of *Pseudallescheria* keratitis successfully treated with this drug. The reasons for the failure of high dose miconazole treatment in this case are unclear, but the administration of topical corticosteroids and lack of drug penetration to the infection site may have contributed.

Only three cases of endophthalmitis due to *P boydii* have been previously reported, none associated with keratitis. In one case of endophthalmitis following cataract extraction[8] the patient recovered after 3 months of topical treatment with amphotericin B, 4 mg/ml 2 hourly. Treatment success may have been due to the anterior location of this infection. In a second case[3] the infection was haematogenous in origin in a woman receiving corticosteroid treatment for lupus nephritis. Parenteral therapy with miconazole was unsuccessful despite the fact that the drug was detected in the vitreous. The third case[9] occurred in a 15-year-old patient who developed aspiration pneumonia and died despite niconazole therapy.

The treatment of mycotic keratitis remains a difficult problem, because none of the available antifungal drugs is ideal. Natamycin has been used successfully to treat filamentous fungal infections, but its tissue penetration is limited and it is ineffective subconjunctivally.[10 11] Nystatin and amphotericin B have been even less successful than natamycin, and both are irritating to the involved tissue.[11] Of the topical imidazoles, econazole has the broadest spectrum[12] and has been used successfully to treat mycotic keratitis due to *Aspergillus* spp and *Fusarium* spp. Miconazole has been used successfully in treating mycotic keratitis both topically[13] and intravenously.[14] Itraconazole has been shown to be useful treating some cases of severe keratitis due to *Aspergillus* spp,[15] but it has proved less successful in eradicating infections caused by *Fusarium* spp and other filamentous fungi.[15 16]

Suspected mycotic keratitis, or mycotic keratitis in which the organism or its sensitivities have not yet been identified, should be treated empirically with a combination of antifungal agents. The broadest such 'best guess' combination treatment should probably include topical miconazole or econazole, subconjunctival miconazole, and either oral itraconazole or intravenous miconazole.

In any case of atypical or indolent keratitis the possibility of fungal infection should be borne in mind, and steroids should be used with great caution, if at all.

We thank Mrs G Bennerson for the photographs.

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British Journal of Ophthalmology, 1992, **76**, 369–371

Nasal and orbital recurrence of conjunctival melanoma 21 years after exenteration

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Accepted for publication
14 November 1991

Abstract

In our experience 5% of invasive malignant melanomas of the conjunctiva arising from areas of primary acquired melanosis with atypia spread to the ipsilateral nasal cavity and paranasal sinuses. Twenty one years after orbital exenteration for multicentric conjunctival melanoma an 82-year-old man was seen with an orbital recurrence, which had extended to the nasal cavity and paranasal sinuses through the nasolacrimal duct without invading the mucosa. This previously undescribed way of spread after the longest symptom-free interval following exenteration ever reported is illustrated.

Malignant melanomas of the nasal cavity or paranasal sinuses which develop in patients with conjunctival melanoma are rare. We report on a patient who was thought to have been cured of conjunctival malignant melanoma of his right eye but presented with an unusual orbital and nasal recurrence 21 years after exenteration of his right orbit.

Case report

A 60-year-old Caucasian man was treated in 1969 by a modified anterior exenteration of the right orbit, a skin splitting technique being used, for multifocal malignant melanoma of the conjunctiva. There was extensive involvement of the caruncle and the inferior palpebral and bulbar conjunctiva. The exenteration specimen showed multiple foci of heavily pigmented malignant melanoma arising from areas of primary acquired melanosis with atypia. The planes of surgical excision were clear of tumour.

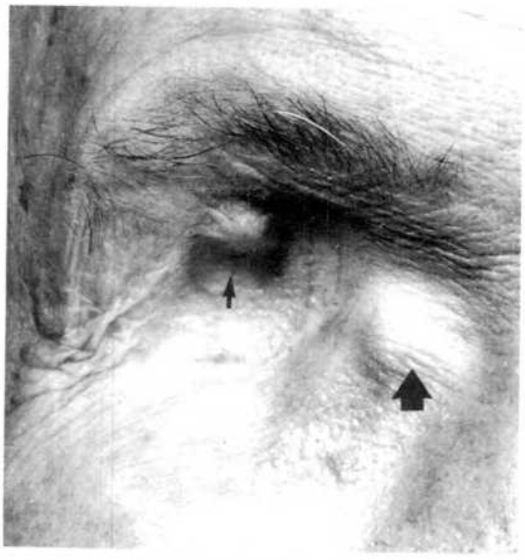

Figure 1 A large subcutaneous recurrence of conjunctival malignant melanoma (large arrow) anteromedially in the right orbit, which had been exenterated 21 years previously. The small, subcutaneous, hard and immobile superolateral nodule (small arrow) remained unchanged over several years and was not associated with the disease.

In 1985 a small, hard subcutaneous nodule, which was tethered to the periosteum superiorly in the right socket, was noted. The overlying skin was slightly pigmented. On observation the small mass remained unchanged.

In 1990, 21 years after the exenteration, the 82-year-old patient complained of obstruction of the right nasal passage. Examination of the right orbit showed a large subcutaneous swelling at the medial edge of the right socket and the pre-existing small nodule at the superolateral edge (Fig 1). Examination of the nasal cavity revealed a large ulcerating pigmented polyp obstructing the right nasal passage (Fig 2). There was no clinical involvement of the regional lymph nodes. Investigation for metastases, including liver ultrasound, liver function tests, and a chest *x* ray, was negative. There was no evidence of cutaneous malignant melanoma. A computerised tomography (CT) scan (Fig 3) showed the presence of tumour in the right anteromedial orbit, the nasolacrimal duct, invasion of the anterior ethmoidal cells, and a large intranasal mass. A diagnostic biopsy of the nasal lesion confirmed the clinical diagnosis of malignant melanoma. The patient's remaining eye showed lens opacities and age-related macular disease, reducing the visual acuity to 6/12.

The patient was treated by right lateral rhinotomy. The skin overlying the medial orbital mass was excised. The anteromedial wall of the maxilla and the orbital floor were removed, and subsequently the tumour was cleared from the

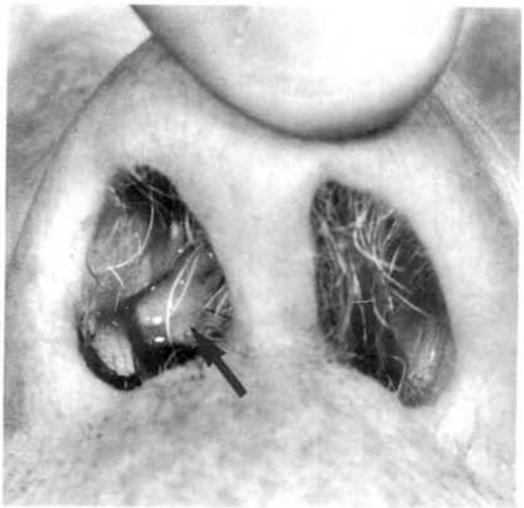

Figure 2 Ulcerating malignant melanoma (arrow) which obstructed the right nasal passage and was connected with the orbital mass through the nasolacrimal duct.

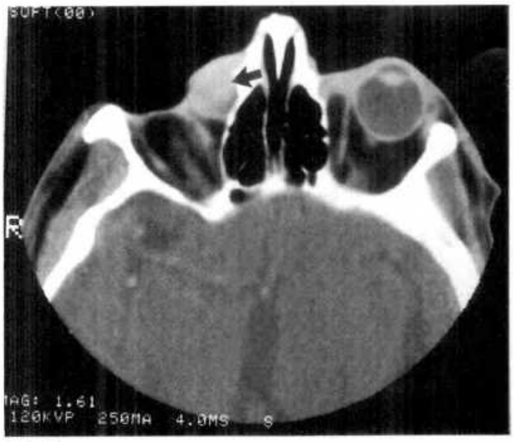

Fig 3A

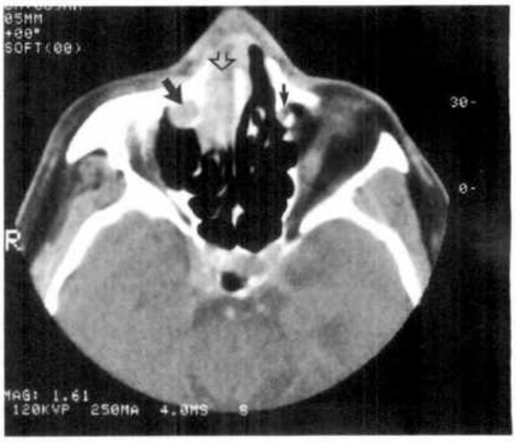

Fig 3B

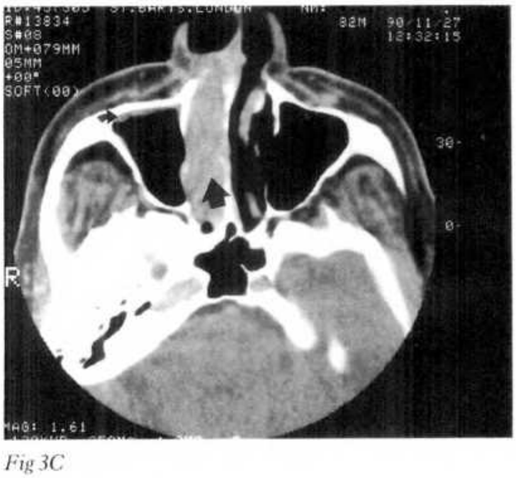

Fig 3C

Figure 3 Orbital axial CT scans. (A) a large soft tissue mass (arrow) lies anteromedially within the exenterated right orbit. Note the residual optic nerve and medial and lateral rectus muscles; (B) the right nasolacrimal duct (large arrow) has been expanded by a soft tissue mass and is 100% larger than its normal counterpart (small arrow). There is a large intranasal mass (open arrow) with invasion of the anterior ethmoidal cells; (C) the nasal soft tissue mass (large arrow) fills the entire nasal cavity with no evidence of residual conchae. The right maxillary antrum shows a thin line of mucosal thickening (curved arrow), which is probably secondary to inflammation. In this section there is no evidence of tumour in the maxillary sinus.

maxillary antrum, the anterior ethmoidal cells, and the nasal cavity. At surgery it became apparent that the nasal element of the disease was a direct extension of the orbital recurrence through the nasolacrimal duct, without invading mucosa or bone. A forehead flap was used to close the orbitonasal defect.

Histological examination of the excised orbital element showed orbital skin with an underlying, well demarcated grey-black nodule with a maximum diameter of 8 mm, consistent with malignant melanoma (Fig 4). The degree of pigmentation varied from amelanotic to deeply pigmented. Histologically the nasal element consisted of similar pigmented tumour, which contained focal spindle areas and showed focal necrosis. Histological study of superolateral orbital skin revealed fibrosis of the dermis but no tumour.

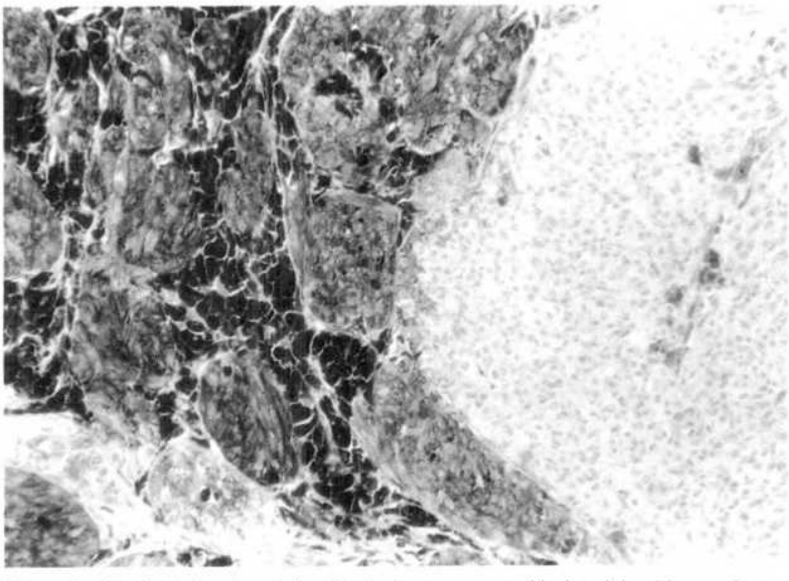

Figure 4 Histological section of the orbital subcutaneous grey-black nodule with a maximum diameter of 8 mm, showing malignant melanoma with varying degrees of pigmentation (haematoxylin and eosin, ×185).

The postoperative course was uneventful, and when the patient was last seen in June 1991 there were no signs of local or regional metastases.

Discussion

Between 1949 and 1991 more than 260 cases of histologically confirmed invasive malignant melanoma of the conjunctiva have been treated in Moorfields Eye Hospital and St Bartholomew's Hospital. Eight cases of malignant melanoma of the nasal cavity and paranasal sinuses complicating malignant melanoma of the conjunctiva have been encountered.

In a previous report[1] on four of these eight cases the nasal melanoma was recognised months to years after diagnosis of the ipsilateral conjunctival melanoma. The maximum interval between last treatment and diagnosis of the nasal tumour was 9 years.[1] In our case the recurrence was diagnosed 21 years after orbital exenteration, which is the longest symptom-free interval reported after such treatment. This finding emphasises the importance of long follow-up periods in the study of conjunctival malignant

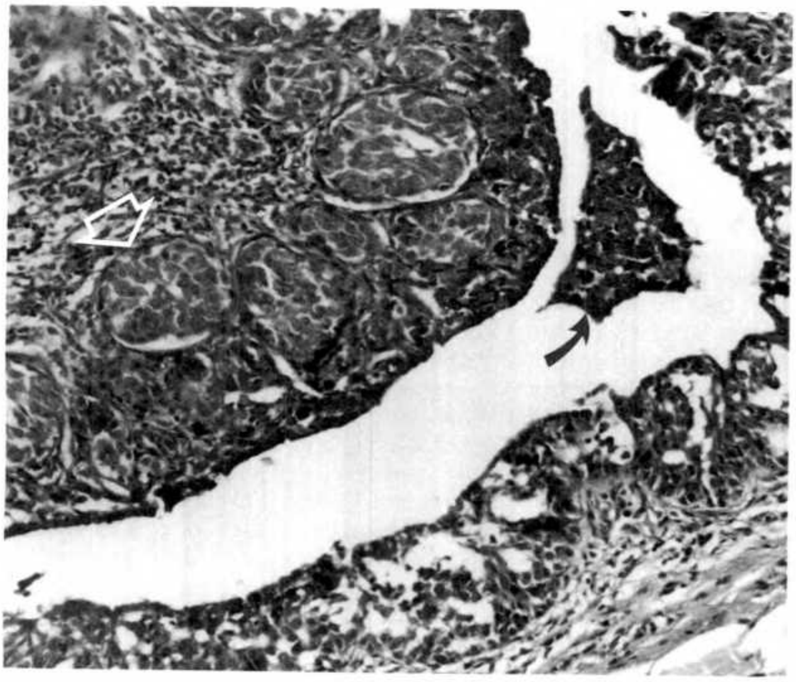

Figure 5 Malignant melanoma cells in the lumen (black arrow) and the wall (white arrow) of the lacrimal apparatus in an exenteration specimen (haematoxylin and eosin, ×300).

melanoma. As no other foci of malignant melanoma were found in this patient, the recurrent tumour probably originated from residual melanocytes with a very low growth rate during 21 years, or which remained quiescent for many years before entering an active growth phase. Exenteration of the orbit results in a maximal nasal clearance of 2 mm or less, which may have been insufficient totally to eradicate the medially located melanoma. The incomplete removal of the posterior orbital structures by the modified anterior exenteration (Fig 3A) could also account for the local recurrence, but the anterior location of the recurrent neoplasm argues against this.

This case also differs from the other cases in our series in that there was a connection between the nasal and orbital elements of the disease through the nasolacrimal duct without invading mucosa or bone. Therefore, the nasal melanoma is more likely to represent a direct extension of the orbital recurrence than a new nasal focus.

It is of interest that in all eight cases of nasal and conjunctival malignant melanoma the initial tumour originated from areas of conjunctival primary acquired melanosis (PAM) with atypia. This multicentric precursor was noted in approximately 60% of our patients with invasive conjunctival malignant melanoma and may pose a higher risk of recurrent disease to the patient. Another risk factor of nasal metastasis may be the location of the tumour. Seven out of eight cases showed involvement of the medial ocular structures, including the medial tarsal or bulbar conjunctiva, the plica and the caruncle. Symptoms of a nasal location of malignant melanoma are recurrent epistaxis or chronic obstruction of the ipsilateral nasal passage, and the clinician should be aware of those symptoms in patients with conjunctival melanomas, especially those that originated from PAM with atypia.

Robertson *et al*[1] proposed that malignant melanomas of the nasal cavity and the paranasal sinuses could evolve from either direct extension along vessels or regional metastases via the blood stream, and they thought it would be less probable that the metastases were caused by dissemination of tumour cells to the nasal cavity through tears. However, Weiss *et al*[2] recently found exfoliated atypical melanocytes in the tear film of a patient with multifocal conjunctival melanoma. This finding demonstrates that shedding of melanoma cells into the tear drainage apparatus does occur, but there has been no evidence that these cells have the propensity to cause metastases. Our case has shown that direct extension through the nasolacrimal duct is another distinct possibility. Such a mode of spread was also observed in another case of conjunctival melanoma.[3] On histological examination of the exenteration specimen we detected atypical melanocytes in the lumen of the lacrimal apparatus (Fig 5). Serial sectioning showed these cells formed part of a stalactite-like extension from the conjunctival tumour.

Punctal occlusion has been suggested to prevent seeding of malignant cells into the lacrimal apparatus,[2] but it would not prevent settling of blood-borne metastases or tumour extension along vessels. Surgical procedures may induce dispersion of melanocytes or may not eradicate all the neoplasm. If multicentric conjunctival melanomas, especially those involving the medial canthus, require orbital exenteration, postoperative external beam radiotherapy[4] with megavoltage photons to the socket and nasolacrimal duct may prevent local metastases in the nasal cavity and paranasal sinuses, a condition which is known to be associated with a poor prognosis.[1 5]

The suggestions of Dr I F Moseley, Department of Radiology, Moorfields Eye Hospital, and Dr M Charlesworth, Department of Radiology, St Bartholomew's Hospital, are gratefully acknowledged. We would like to thank Dr C Wells, Department of Pathology, St Bartholomew's Hospital, for kindly providing the histological sections.

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British Journal of Ophthalmology, 1992, **76**, 372–374

Pseudopapilloedema in the linear naevus syndrome

S H Campbell, A Patterson

Abstract

This case report describes the ophthalmic findings in a child with the linear naevus syndrome. The patient was referred by the Department of Paediatric Neurology with 'unilateral papilloedema'. This was thought to be a form of pseudopapilloedema, a finding that has not been previously described in this syndrome.

The linear naevus syndrome is a rare condition first described by Jadassohn in 1895.[1] Other names include the epidermal naevus syndrome, the sebaceous naevus syndrome,[2] the naevus of Jadassohn, Feuerstein-Mimms syndrome,[3] oculo-neuro-cutaneous syndrome of Schimmelpenning,[4] organoid naevus phacomatosis,[5] Solomans's syndrome,[6] and several combinations of the above.[7-9]

Case report

A male child born in 1982 following a normal pregnancy was noted at birth to have a cyst in his mouth and a blister on the lip. Several weeks after birth a patch of pigmented, hyperkeratotic skin developed below the chin on the left side extending from behind the ear down onto the neck. The blister on the lip became more obvious and was noted to blanch. At the age of 13 months he started having seizures and there was developmental delay.

A dermatological opinion was sought on the nature of the skin lesion. Several areas of epidermal, sebaceous naevi on the face, lips, and left side of the neck were noted.

An ophthalmic opinion noted an intermittent, divergent squint with equal fixation with each eye and normal fundi. A paediatric dental opinion reported hypoplasia/hypocalcification of teeth.

A computed tomographic (CT) scan demonstrated an extensive low density lesion in the left frontal lobe containing one small nodule of calcification. There was no displacement of mid-line structures.

An EEG showed abnormalities of both hemispheres, particularly the left, with multifocal discharges and excess of irregular slow-wave activity.

A left internal carotid angiogram was performed and showed no evidence of pathological circulation or other abnormality. By 1985 a mild right hemiparesis with hemianopic inattention on the affected side and mental retardation were apparent. A repeat CT scan showed no change. In 1990 left unilateral papilloedema was noted. A CT scan showed little change (Fig 1) although there was some midline shift. The CT appearances were consistent with the mild right hemiparesis and hemianopic attention defect. Magnetic resonance image (MRI) scanning was not considered likely to yield further useful information.

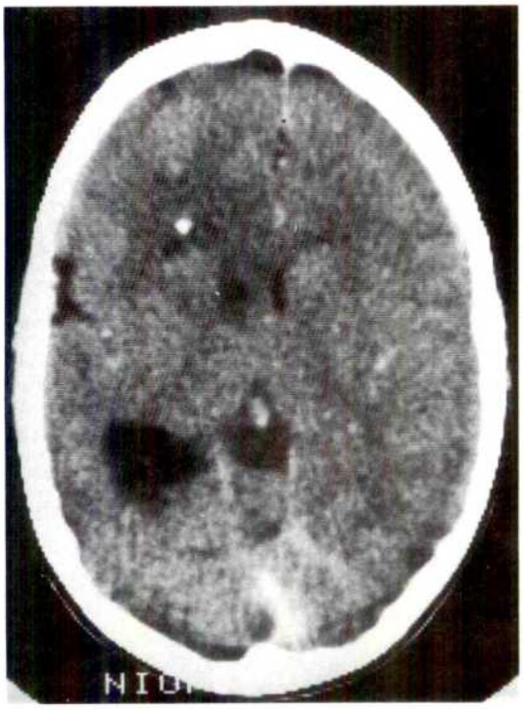

Figure 1 CT scan demonstrating low density lesion in the left frontal lobe with nodule of calcification.

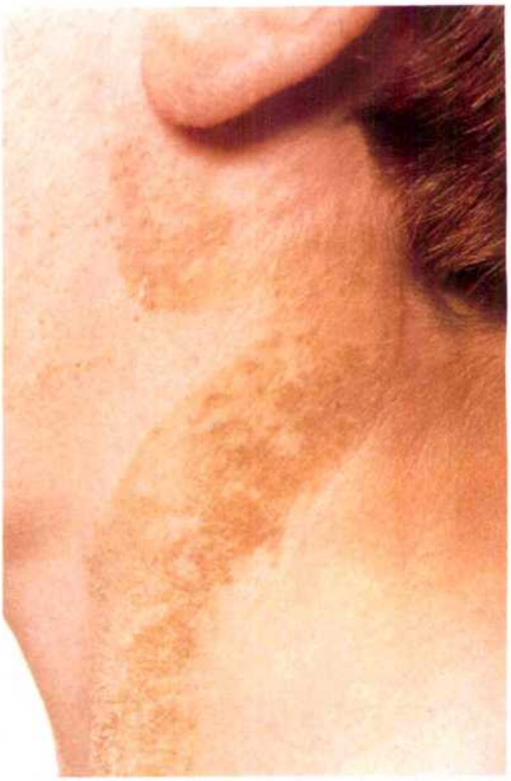

Figure 2 Linear sebaceous naevus on the left side of the neck.

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Accepted for publication
27 September 1991

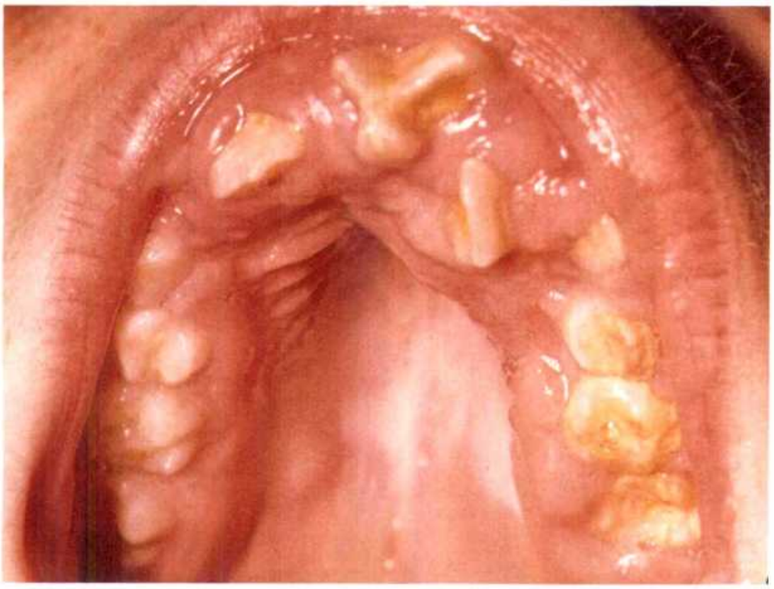

Figure 3 Abnormal dentition and enlarged lips on the left.

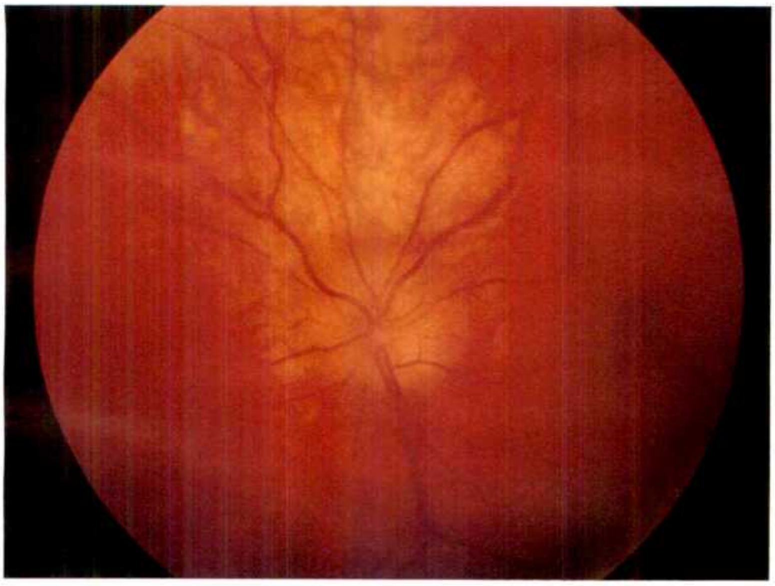

Figure 4 Left optic disc swelling.

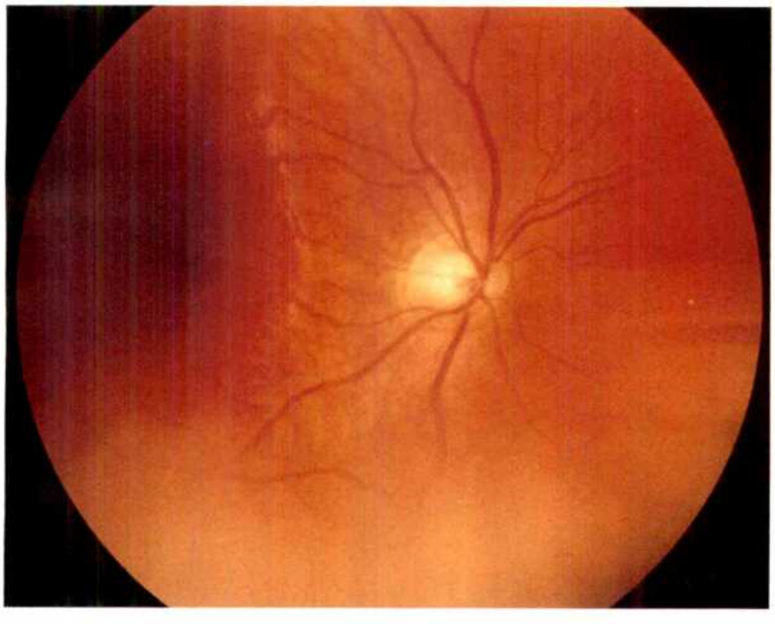

Figure 5 Temporal pallor of right optic disc.

The most recent CT scan (August 1991) showed no change in the calcification or the low density area occupying most of the frontal lobe. There was no alteration in the position or size of the ventricles and no abnormality of the optic nerves. The child was referred for an ophthalmic opinion.

Ocular history was of an intermittent squint, the left eye turning out since birth, especially when tired. Examination revealed the linear sebaceous naevus on the left side of the neck (Fig 2), and the abnormal dentition (Fig 3). Visual acuities were 6/6 left and right. Orthoptic examination demonstrated a simulated distance exotropia, measuring 14 prism dioptres base in at one third of a metre and 45+ dioptres base in at 6 metres and 15° on the synoptophore. Gross binocular function was preserved. There was some right hemianopic inattention. Ocular movements and pupil responses were normal and there were no cranial nerve defects. Cycloplegic refraction was +0·5 DS right and left. Fundi showed left optic disc swelling (Fig 4) and temporal pallor of the right optic disc (Fig 5).

Discussion

The linear naevus syndrome, although rare, is of interest to several of the clinical specialities including ophthalmology. Mansour *et al*[2] describe the syndrome as manifesting skeletal, neurological, vascular, and dermatological disorders. The skin lesions are congenital, epidermal, linear, and rarely cross the midline. They tend to occur on the head and face and are of two types. Linear epidermal naevi are characterised by brown linear unilateral papules with hyperpigmentation and hyperkeratosis. When the lesions have many sebaceous glands they are called sebaceous naevi. These have been known to undergo malignant change early in life, and are also associated with systemic malignancies. Ocular findings are detailed by Mansour *et al*[2] and Taylor[9] and include ptosis, conjunctival dermoids, colobomas, and Coats' disease.

Taylor lists the aetiology of unilateral optic disc swelling in childhood under six headings: pseudopapilloedema, tumours (involving the optic nerve head), uveitis, ischaemic optic neuropathy, papillitis, and papilloedema which may be asymmetrical. The most likely explanation in this case is pseudopapilloedema. Buried drusen are the commonest cause and have been described in numerous and diverse ocular and neurological disorders including tuberous sclerosis. Glial anomalies of the optic disc head are another possibility. Optic nerve head drusen may be detected by their autofluorescence, and on fluorescein angiography, when they hyperfluoresce but do not leak dye. CT scanning will demonstrate large calcified drusen. Unfortunately in this case angiography was not possible due to the patient's age and developmental delay. A recent CT scan of the optic nerves did not demonstrate the presence of disc drusen.

Some authors have called the syndrome the fifth phacomatosis.[7] However with the inclusion of Wyburn-Mason syndrome along with Von

Hippel Lindau disease, Sturge Weber syndrome, tuberous sclerosis and neurofibromatosis, it becomes the sixth member of this diverse group. The conditions are characterised by disseminated hamartomas, with a predilection for the central nervous system, retina, and skin, hence the term 'phakomatosis' or 'mother spot'. Hamartomas are tumours composed of cells normally present in the involved tissue. Certainly our case has cutaneous and probably oral hamartomas. The nature of the CNS lesion remains unclear. The most likely diagnosis is that it represents a very low grade glioma. Another possibility is a localised grey/white matter migration defect, although this would not explain the calcification.

The authors thank Paul Bloor, ophthalmic medical photographer for providing the photographs.

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British Journal of Ophthalmology, 1992, 76, 375–379

Fundus albipunctatus associated with cone dystrophy

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Accepted for publication 15 November 1991

Abstract

We describe five unrelated patients in whom the typical signs of fundus albipunctatus were accompanied by colour vision defects, bull's eye or similar macular lesions, and severely diminished full-field cone electroretinograms indicating widespread damage to cones outside the macula. All patients had noticed night blindness from childhood. Signs of retinitis punctata albescens, a disease of similar appearance but with characteristics resembling retinitis pigmentosa, were absent. We cannot be sure whether these patients represent a process of fundus albipunctatus or a distinct disease entity or a casual combination of fundus albipunctatus and cone dystrophy.

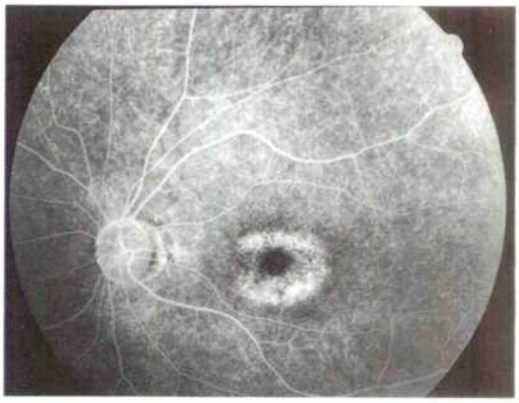

Fig 1B

Fundus albipunctatus is a stationary disorder characterised by myriads of yellow-white dots in the fundus and an abnormally slow rate of dark adaptation.[1-6] The electroretinograms (ERGs) require a much longer dark adaptation time than normal to reach maximum amplitude.

Some reports have described cases of macular degeneration associated with fundus albipunctatus.[1 7-10] In the past 10 years we have had five patients in whom apparent fundus albipunctatus was associated with macular degeneration. In all the patients the rod function showed characteristic properties of fundus albipunctatus, but full-field cone ERGs showed significant reduction.

Case reports

The five unrelated patients had noticed night blindness from childhood. The anterior segment, lens, and vitreous were normal in all patients, and none showed nystagmus or strabismus. The results of general physical examinations and routine laboratory tests were also normal.

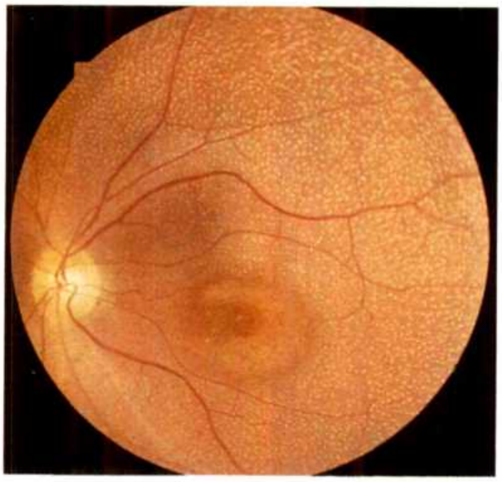

Fig 1A

Figure 1 Fundus photograph (A) and fluorescein angiography (B) of the left eye in case 1.

CASE 1

A 49-year-old man with night blindness had noticed reduced vision over the previous 6 years; his corrected visual acuity was 0·6 in each eye. No one with night blindness or severely low vision was found in his pedigree. His healthy parents were first cousins.

Discrete, dull white, uniform, dot-like lesions, seen over much of the fundi, were of great density in the midperiphery of both eyes (Fig 1A). The maculae each showed a bull's eye lesion. No attenuation of retinal vessels, optic atrophy, or pigmentary clumping was seen. Fluorescein angiography revealed irregular, spotty hyperfluorescence in the midperiphery, which did not correspond to the flecks; the macula showed ring-shaped hyperfluorescence (Fig 1B). Visual fields were tested with the Goldmann perimeter using 3 ioptres. The peripheral visual fields were normal, but central sensitivity was slightly decreased in both eyes. Colour vision tests revealed severe blue-yellow and red-green defects. Dark adaptation was tested by using the Goldmann-Weeker adaptometer in the right eye. A white test target of 11° was presented at 15° of the upper retina. After 30 minutes the visual threshold was approximately 5 log units higher than normal. After 3 hours it remained 0·5 to 1·0 log unit higher than normal.

Full-field ERGs of the right eye (Fig 2) were made by the standard recording technique previously described.[11] The mean (with 2 SD) amplitudes in the normal subjects after 30 minutes of dark adaptation were 325 (140) μV (scotopic (rod) b wave), 59 (21) μV (photopic (cone) b wave), and 38 (19·1) μV (30 Hz flicker responses). After 30 minutes of dark adaptation (Fig 2, upper tracings in case 1), no scotopic

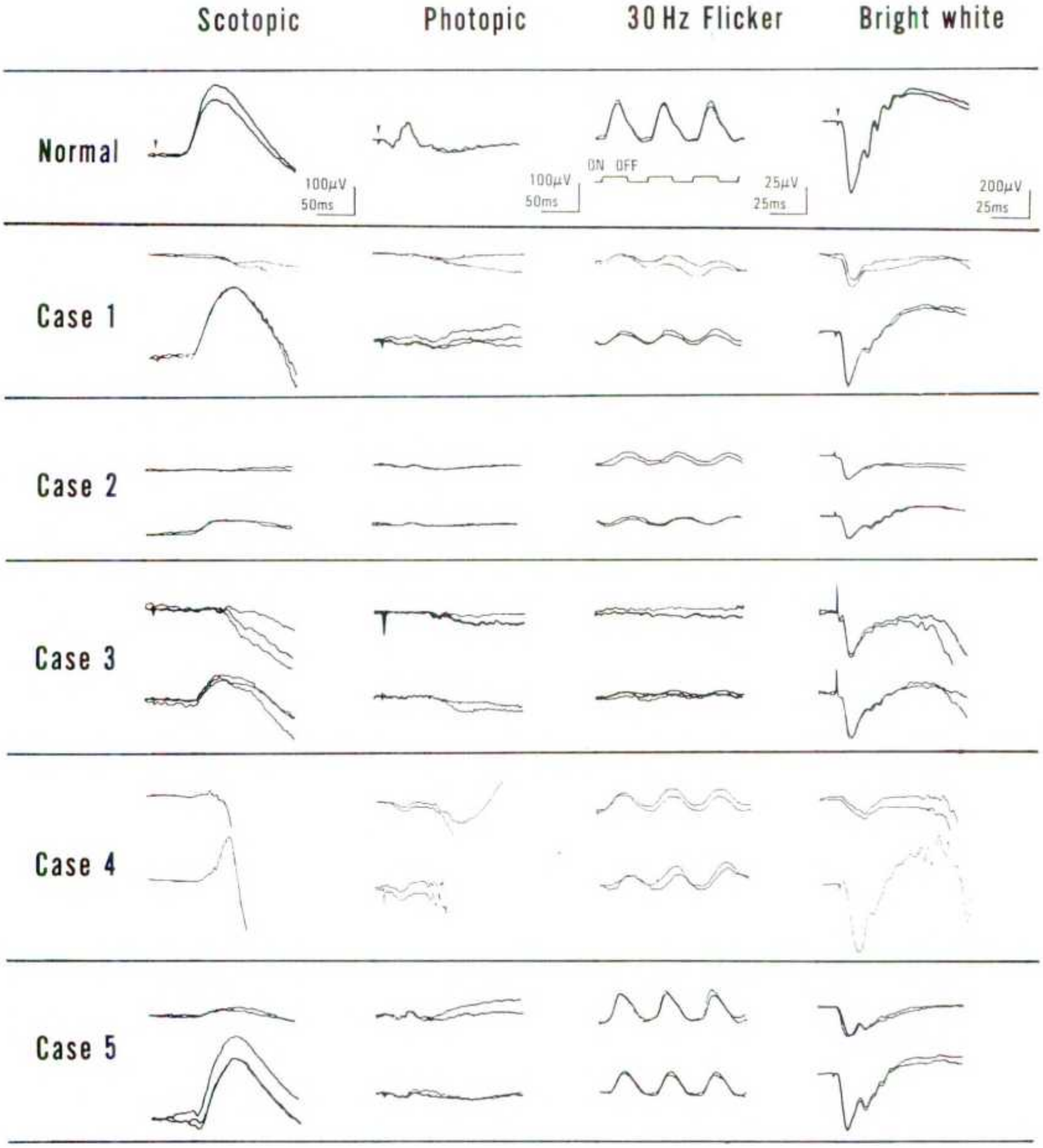

Figure 2 Full-field electroretinograms of a normal subject and cases 1 to 5. In each case the upper tracings indicate the responses recorded after 30 minutes of dark adaptation; the lower tracings indicate the responses recorded after prolonged dark adaptation (see text for the details). The arrows indicate the stimulus onset.

(rod) or photopic (cone) ERG was recordable. The amplitudes of 30 Hz flicker responses were 9·6 μV with the delayed implicit time. A single bright-flash (white bright) ERG showed severely decreased b wave and moderately decreased a wave. After 3 hours of dark adaptation (Fig 2, lower tracings in case 1), rod b wave was 291 μV in amplitude with normal implicit time. The cone b wave was 16·6 μV in amplitude with delayed implicit time. The 30 Hz flicker responses showed little change in comparison with those recorded after 30 minutes of dark adaptation. A single bright-flash ERG showed normally shaped a waves and b waves.

An electro-oculogram (EOG) was recorded as described previously.[11] The light peak versus dark trough ratio was 1·42 (right eye) and 1·37 (left eye). A statistical analysis of normal subjects indicates that a ratio smaller than 1·80 is abnormal.

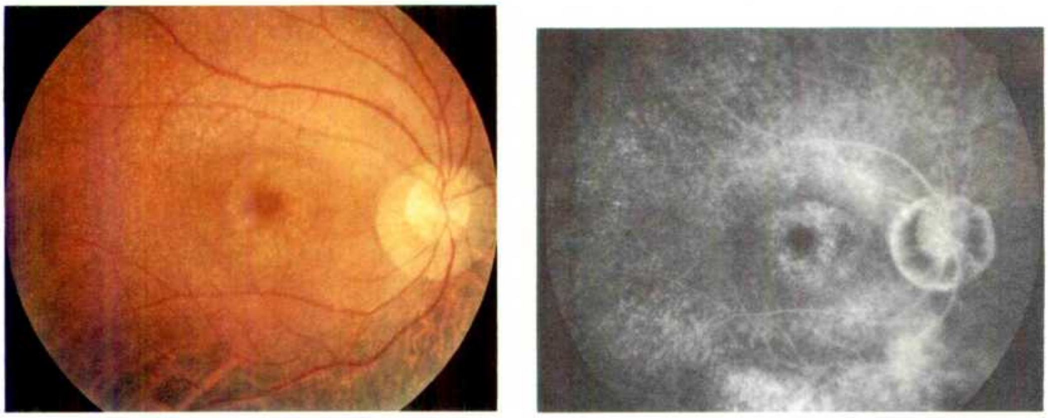
Fig 3A *Fig 3B*

Figure 3 Fundus photograph (A) and fluorescein angiography (B) of the right eye in case 2.

CASE 2

A 49-year-old man with night blindness first noticed blurred vision and metamorphopsia in both eyes in 1987. In 1989 his corrected visual acuity was 1·2 (right eye) and 1·0 (left eye), and in 1990 it was 0·6 (right eye) and 1·0 (left eye). No patient with night blindness was found in his pedigree, and his parents were not consanguineous.

The fundus and fluorescein angiography findings (Figs 3 A, B) were similar to those of case 1. However, a localised, symmetrical chorioretinal atrophy was noted in the nasal inferior fundus of both eyes. Suggestive attenuation of retinal vessels was observed, and the optic disc was normal in both eyes. The peripheral visual fields were normal except for a depression in the area corresponding to the chorioretinal atrophy; the central visual fields each had an annular scotoma. Colour vision tests revealed a severe blue-yellow defect and moderate red-green defect. The visual threshold was 3·8 log units higher than normal after 30 minutes of dark adaptation and was 2·5 log units higher than normal after 1 hour of dark adaptation.

In full-field ERGs recorded in the right eye after 30 minutes of dark adaptation (Fig 2, upper tracings in case 2), rod b wave was unrecordable, while cone b wave (15 μV) and 30 Hz flicker responses (9·6 μV) were extremely reduced with delayed implicit time. A single bright-flash ERG showed severely decreased b and moderately decreased a waves. After 1·5 hours of dark adaptation (Fig 2, lower tracings in case 2) the rod b wave was recorded with an amplitude of 67 μV with normal peak time. Single bright-flash electroretinography recorded increased b wave amplitude. The cone and 30 Hz flicker responses were not significantly different from those recorded after 30 minutes of dark adaptation.

The EOG ratios were 1·75 (right eye) and 1·64 (left eye).

CASE 3

This patient with night blindness was first examined by us in 1981 at the age of 40. There was no notable family history except that his parents were first cousins. The fundus appeared to be typical of fundus albipunctatus, and the maculae were normal ophthalmoscopically. In 1984 we found some pigmentary clumpings in the nasal inferior area of the right eye which developed into local chorioretinal atrophy during a further 6-year follow-up.

In 1989 we noted ophthalmoscopic changes, suggestive of early bull's eye maculopathy, in the maculae of both eyes (Fig 4). Fluorescein angiography also showed suggestive, ring-shaped hyperfluorescence.

In 1990 the visual acuity was 1·2 in each eye. The peripheral visual fields showed depression only in the area corresponding to the chorioretinal atrophy in the right eye. The central field showed slightly decreased central sensitivity in both eyes. Colour vision tests revealed a moderate blue-yellow defect and mild red-green defect. The visual threshold during dark adaptation was 4·0 log units higher than normal after 30 minutes of dark adaptation, but reached a normal level after 3 hours of dark adaptation.

Full-field electroretinography (Fig 2, upper tracings in case 3) did not record rod, cone, or 30 Hz flicker responses after 30 minutes of dark adaptation. A single bright-flash ERG showed mildly and severely reduced a and b waves, respectively. After 3 hours of dark adaptation (Fig 2, lower tracing in case 3) a rod b wave of amplitude of 116 μV with normal peak time was recorded. Cone b wave and 30 Hz flicker responses were extremely small, with the amplitudes of 14 μV and 12 μV, respectively, with the delayed implicit times. Single bright-flash electroretinography showed increased b wave amplitude.

The EOG ratios were 2·52 (right eye) and 2·23 (left eye).

CASE 4

In 1984 a 34-year-old man with night blindness visited our clinic because he noticed reduced vision in his left eye; visual acuity was 1·0 (right eye) and 0·4 (left eye). In 1988 the visual acuity was 1·0 (right eye) and 0·1 (left eye). His younger brother complained of night blindness, but was not examined. Their parents were not consanguineous.

His fundus (Fig 5A) contained multiple yellow-white dots mainly in the midperiphery; the maculae showed well circumscribed chorioretinal atrophy of 1·5 disc diameters, which spared the foveola in the right eye (Fig 5B). The optic disc was normal, and the retinal vessels were not attentuated. No pigment clumps were seen in the fundus. The visual fields were essentially normal except for a central scotoma of 7° to 9° detected in each eye. Colour vision tests indicated severe red-green defect and moderate blue-yellow defect. The dark adaptation curve was 4·7 log units above normal threshold after 30 minutes and 2 log units above normal after 2 hours of dark adaptation.

Full-field ERGs after 30 minutes of dark adaptation (Fig 2, upper tracing in case 4) showed no rod response and reduced cone b wave and 30 Hz flicker responses (25 μV and 15·4 μV, respectively). The implicit times of cone b wave and 30 Hz flicker responses were delayed. Single bright-flash electroretinography recorded reduced a and b waves. After 2 hours of dark adaptation (Fig 2, lower tracings in case 4) rod b wave was recorded (amplitude,

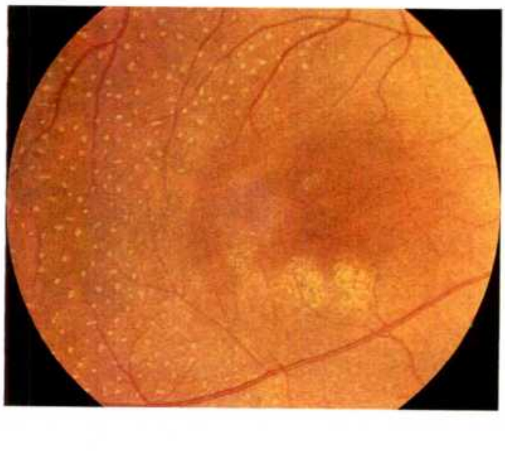

Figure 4 Fundus photograph of the right eye in case 3.

Figure 5 Fundus photograph (A) and fluorescein angiography (B) of the left eye in case 4.

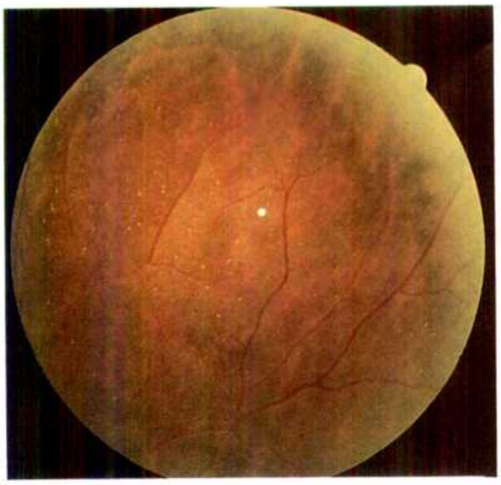

Fig 5A

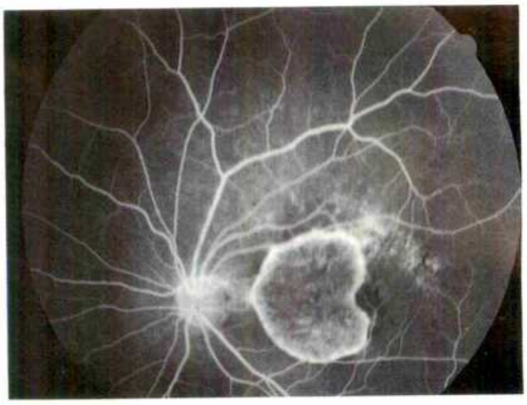

Fig 5B

192 μV) with normal implicit time. The cone b wave and 30 Hz flicker responses showed no significant change after 2 hours' dark adaptation; single bright-flash ERG showed an increase in amplitude of a waves and b waves.

The EOG ratios were normal: 1·86 (right eye) and 2·15 (left eye).

CASE 5

A 37-year-old woman with night blindness noticed reduced vision about 10 years ago. In 1987 her corrected visual acuity was 0·8 (right eye) and 0·4 (left eye). Her pedigree contained no other patient with night blindness or low visual acuity, and her parents were not consanguineous.

Fundus examination (Fig 6A) revealed multiple white dots in the midperiphery and non-specific degeneration of the macula. Fluorescein angiography showed irregular hyperfluorescence in the macula (Fig 6B). The peripheral visual field was full, and the central field showed slightly decreased sensitivity. Colour vision tests indicated severe red-green and moderate blue-yellow defects. The dark adaptation curve was 5·5 log units above normal threshold after 30 minutes of dark adaptation but was normal after 3 hours of dark adaptation In full-field ERGs recorded after 30 minutes of dark adaptation (Fig 2, upper tracings in case 5), the amplitudes were 33 μV (rod b wave), 30 μV (cone b wave) and 27 μV (30 Hz flicker responses). Their implicit times were normal. Single bright-flash electroretinography revealed moderately reduced a wave and severely reduced b wave. After 3 hours of dark adaptation the rod ERG and a single bright-flash responses were normal. Cone ERG and 30 Hz flicker responses, however, remained unchanged.

Discussion

The five patients described here had ocular signs of both fundus albipunctatus and cone dystrophy. Bull's eye or similar macular lesions were present, and full-field cone electroretinograms demonstrated that damage to cones was not limited to the macula, but was widespread as in cone dystrophy. All patients had noticed night blindness from childhood. They started to notice decreased visual acuity from the second or the third decade, and we therefore believe that the cone impairment is progressive. All these patients had severe colour vision defects, even though some of them had relatively good visual acuity.

Fundus albipunctatus with macular degeneration has been reported by other authors.[1,7-10] Detailed ocular examinations of two patients[9-10] yielded findings similar to ours. The fundi of these patients displayed multiple yellowish white dots, and the maculae showed bull's eye maculopathy. Recovery of rod function was abnormally delayed and cone electroretinograms showed severe impairment.

Retinitis punctata albescens is a hereditary dystrophy which produces white dots in the fundus and the clinical and electrophysiological characteristics of retinitis pigmentosa.[12,14] The punctate lesions are similar to those in fundus albipunctatus, but the fundus also shows diffuse atrophy of the retinal and pigment epithelium,

Figure 6 Fundus photograph (A) and fluorescein angiography (B) of the left eye in case 5.

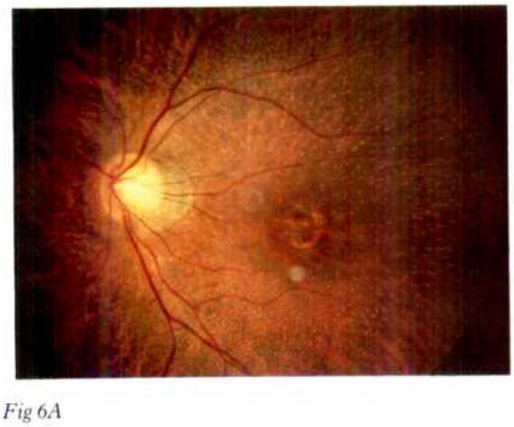

Fig 6A

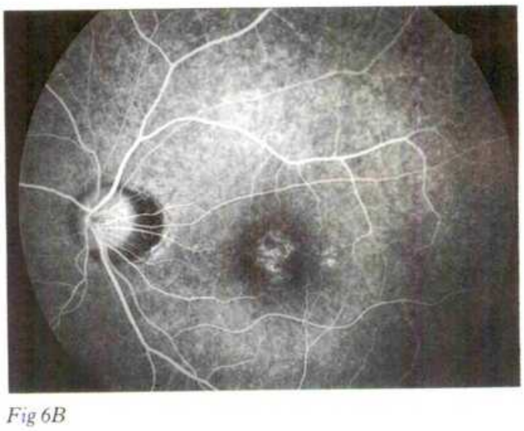

Fig 6B

arterial narrowing, disc pallor, and often some black pigment spicules. The symptoms include permanent night blindness, peripheral field loss, and sometimes a loss of central vision. Some authors consider that these disorders form a continuum, but convincing evidence indicates they are separate entities. Using fundus reflectometry to study two brothers with fundus albipunctatus, Carr and associates[15] noted that the slow dark adaptation that characterised the disorder clinically corresponded to an abnormally slow rate of visual pigment regeneration. Thus our concept of fundus albipunctatus and retinitis punctata albescens is that the former is a stationary disorder of visual pigment regeneration, while the latter is a progressive dystrophy that permanently damages the photoreceptors and pigment epithelium.

Our patients did not have retinitis punctata albescens, because they had abnormally delayed recovery of rod function, no attenuation of retinal vessels (only case 2 showed suggestive attenuation of retinal vessels), no disc pallor, and a normal or only slightly constricted peripheral visual field. Moreover, it should be noted that the rod b wave after prolonged dark adaptation showed normal implicit time in all patients. It seems more likely that fundus albipunctatus was associated with cone dystrophy. Two of our patients (cases 2 and 3) showed some pigment spicules, localised in the midperipheral retina. Cone dystrophy may also show such changes during the course of progression.[1] In the advanced stage of cone dystrophy rods may also be affected, retinal vessels become attenuated, and pigment clumps and diffuse atrophy of the retinal pigment epithelium become apparent. Once these characteristics have developed, the differential diagnosis from retinitis punctata albescens may not be easy.

At present we cannot establish unequivocally whether these patients represent a process of fundus albipunctatus or an independent clinical entity or simply the combined manifestations of two different diseases.

Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, USA, 30 April 1991.

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British Journal of Ophthalmology, 1992, **76**, 380–382

Titanium tetrachloride burns to the eye

D K Chitkara, B J McNeela

Abstract

We present eight cases of chemical burns of the eyes from titanium tetrachloride, an acidic corrosive liquid. However it causes severe chemical burns which have a protracted course and features more akin to severe alkali burns. Injuries related to titanium tetrachloride should be treated seriously and accordingly appropriate management is suggested.

The effect of chemical injuries to the eye is well documented.[1-3] Titanium tetrachloride ($TiCl_4$) is an intermediate product in the manufacture of the widely used pigment titanium dioxide (TiO_2). TiO_2 is a white inert pigment used in the manufacture of paints, linoleum, lacquers, leather, inks, rubber, soaps, textiles, ceramics, plastics, and numerous other consumer, commercial, and building products. It is also used in adhesives, cellophane, cosmetics, paper products, and to whiten salads and spreads.

Titanium tetrachloride is a corrosive pale yellow liquid which is acidic. When exposed to the atmosphere it gives off dense white fumes composed of hydrogen chloride mist and solid particles of hydrolysed titanium compounds.[4] Major chemical burns caused by $TiCl_4$ do not follow the pattern of injury and healing that would normally follow injury by a corrosive acid – for example, hydrochloric acid or sulphuric acid. Instead, to some degree the severity of injury is consistent with an injury caused by a strong alkali – for example, ammonia or sodium hydroxide.

We present eight cases of $TiCl_4$ burns to the eye which have been seen in our casualty department over the past 4 years, four of which illustrate this compound's propensity for severe tissue damage. The cases are described in detail and summarised in Table 1. Thoft's classification[5] has been used to grade the injuries.

Case reports

CASE 1

A 20-year-old man accidently splashed $TiCl_4$ liquid in his left eye. On examination the vision was reduced to 6/36+1 and there were mild corneal and inferior conjunctival epithelial defects in his left eye. The patient was treated with betamethasone with neomycin and atropine drops. He made an uneventful and complete recovery and was discharged 2 days later.

CASE 2

A 39-year-old man was accidently sprayed on his face by $TiCl_4$ from a high pressure pipe. Fortunately he was wearing goggles and only suffered Thoft grade I burns to both eyes. He was treated with topical steroids and antibiotics and made an uneventful recovery within 3 days. He also suffered severe burns to both his calves and face, requiring split skin grafts.

CASE 3

A 19-year-old man accidentally splashed a small amount of $TiCl_4$ onto both eyes. He suffered mild corneal punctate stains which recovered completely and uneventfully within 2 days following treatment with chloramphenicol eye ointment.

CASE 4

A 46-year-old man was accidentally sprayed with $TiCl_4$ liquid from a high pressure pipe while opening a valve. He suffered Thoft grade 4 corneal and conjunctival burns, especially in the right eye. Intensive treatment with topical steroids and antibiotics was given. The left eye healed rapidly within 3 days. The right eye subsequently developed a sterile hypopyon and raised intraocular pressure. This resolved slowly over a 17 day period. A small corneal epithelial defect remained. Healing was further complicated by upper and lower lid entropion and trichiasis. This progressed to corneal scarring and vascularisation over a 6 week period with persistently raised pressure. Vision deteriorated over several months to perception of light and the eye became totally blind and painful within 2 years. The patient left the district but is known to have undergone enucleation of this eye.

CASE 5

A 42-year-old man accidentally sprayed $TiCl_4$ onto both eyes. The left eye suffered Thoft grade 1 burns, which settled quickly within 3 days. The right eye, however, had Thoft grade 4 corneal and conjunctival burns with conjunctival ischaemia and anterior uveitis. Lens opacity was noted within 3 days. A sterile hypopyon and severe corneal stromal lysis developed in 2 months. This progressed to right corneal perforation despite intensive therapy. The perforation was initially treated with cyanoacrylate glue and a lamellar patch graft. Several attempts at entropion and trichiasis correction were made. The right eye became blind and irritable, and was later enucleated.

CASE 6

A 42-year-old man accidentally sprayed $TiCl_4$ liquid into both eyes and face. The right eye was affected more severely. On presentation there was a large central corneal epithelial defect together with stromal oedema. There was severe

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Accepted for publication
21 February 1992

Table 1 Summary of cases reported

Case no	*Age*	*Sex*	*Laterality*	*Initial VA*	*Severity grade*	*Complications*	*Final VA*
1	20	Male	Left	6/36	2	None	
2	39	Male	Left	6/6	1	None	6/6
			Right	6/9	1	None	6/9
3	19	Male	Left		1	None	
			Right		1	None	
4	46	Male	Left		2	None	
			Right		3	Hypopyon, glaucoma, entropion, trichiasis, corneal scarring and vascularisation, enucleation	
5	42	Male	Left	6/6	1	None	6/6
			Right	CF	3	Cataracts, hypopyon, corneal perforation, entropion, trichiasis	NPL
6	42	Male	Left	6/60	2	None	6/60
			Right	6/60	3	Corneal neovascularisation, symblepharon, entropion, trichiasis and pseudoterygium	CF
7	21	Male	Right		2	None	
8	32	Male	Left	Unobtainable	4	Pulmonary oedema	Died 2 weeks after injury
			Right		3		

CF=counting fingers; NPL=no perception of light.

chemosis and ischaemia of conjunctiva inferonasally. The eye settled slowly and despite intensive therapy the patient developed corneal vascularisation and cicatricial changes in both upper and lower fornices within a matter of 3–4 weeks. Six months after injury he was noted to have symblepharon formation affecting the inferomedial fornix together with a cicatricial entropion and large pseudopterygium covering the nasal cornea which involved the visual axis. Subsequent treatment has included dissection of pseudopterygium with 'Z' plasty of conjunctiva and a free conjunctival graft from upper fornix plus a lamellar corneal graft in May 1988. In March 1989 he had a buccal membrane graft to medial fornix and tarsal entropion correction. This patient is currently under review and further corneal surgery is planned.

CASE 7

A 21-year-old man received an accidental splash of $TiCl_4$ in his right eye. After thorough irrigation he was found to have signs of a Thoft grade 2 chemical burn. There were defects of the inferior corneal and conjunctival epithelium. The epithelial defects healed quickly, but for the next 6 months there was persistent vascular engorgement of the conjunctiva. The response to topical steroid administration appeared to be good, but there was evidence of non-compliance and eventually the inflammation settled after subconjunctival steroid was injected. This patient suffered no permanent visual loss. He was examined 2 years after the injury and no significant abnormality was found.

CASE 8

This patient was admitted to the intensive care unit of a local district general hospital after he was splashed over the whole of his body with $TiCl_4$. This occurred when a large quantity of the chemical was released accidentally at a nearby chemical works. He suffered extensive burns to facial skin, nasopharynx, and larynx. Both eyes were severely injured. The corneas were thick and opaque and there was extensive swelling of the bulbar conjunctiva and episclera. Over the following 14 days there was some clearing of the corneal opacification in the right eye, but the left eye did not improve. It quickly became apparent that this patient had suffered severe injury to the lungs by inhalation of $TiCl_4$ fumes. There was progressive deterioration in pulmonary compliance and it became impossible to maintain adequate oxygenation. He died 2 weeks after the chemical injury. Unfortunately the eyes were not retained at necropsy and histological examination was not performed.

Discussion

Titanium tetrachloride reacts extremely vigorously with water in any form, including perspiration on skin, moisture in air, tears, etc, liberating large quantities of heat. It is postulated that the initial thermal burn exposes the deeper tissues to the effect of hydrochloric acid thereby producing very severe burns. Its effect on skin and lungs are well known.[6 7] Action to deal with eye injury from $TiCl_4$ must be swift. Excess liquid be wiped away immediately with a clean dry cloth to reduce its interaction with water. The eye should then be washed continuously with copious quantities of water for at least 30 minutes, ensuring that irrigation is complete by holding the eyelids open.[8-10] Any solid particles retained under the eyelids must be removed from the eye. All such injuries should then be referred to an ophthalmologist without delay.

After transfer to the hospital irrigation should be repeated. Subsequent management depends on the severity of injury. In instances where a high pressure spray is involved the injury is likely to be very severe due to the combined effects of thermal and strong acid burns. These require intensive topical steroids and ascorbate, topical antibiotics and mydriatics, and oral ascorbate. The examining ophthalmologist should look for cutaneous burns and should be aware of possible respiratory tract injury if the vapour has been inhaled.

The workforce must be made aware of the potential dangers of this chemical. The locations of an eyewash station must be clearly marked around the factory. All workers handling this chemical or working near pipes carrying this chemical should be advised to wear protective clothing and goggles at all times. All the cases, except case 2, in our study were not wearing protective eyewear at the time of injury. In this respect our findings have been conveyed to the manufacturers and efforts have been made to improve safety. No further cases have been referred for at least 1 year.

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LETTER TO THE EDITOR

Alternative method for laser treatment of superior retinal tears in eyes with gas tamponade

SIR,—Intraocular injection of slow absorbing gases either as a primary procedure or in addition to conventional buckling operations has become widespread.

While the tamponade obtained by the intraocular gas is sufficient for closure of retinal tears and absorption of subretinal fluids, it does not detract from the need for either cryo or photocoagulation in order to obtain stable retinal attachment following an initial attachment of the retina.[1] Laser treatment of a retinal tear in the superior 2 o'clock position through a gas bubble is, however, sometimes difficult. The multiple curved refracting surfaces and the flattening effect of the gas on the tear's edges make the tear at times difficult to localise. To overcome this problem the patient's head is tilted to the side at the slit-lamp, thus moving the gas bubble to one side and allowing a view of the tear unhindered by a gas interface.[2] We found this manoeuvre to be difficult for some patients who cannot tilt their head enough, especially when the tear is located in the superior 2 o'clock position.

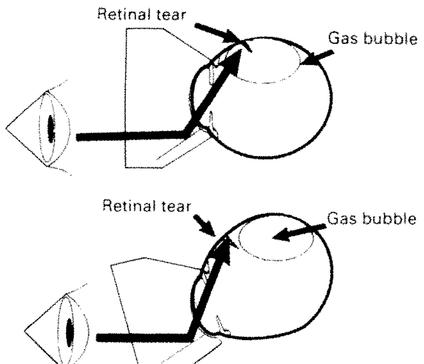

Figure 1 Upper: the eye looks straight ahead and the intermediately tilted mirror (67°) of the three mirror contact lens is best suited for viewing anteriorly located tears. Lower: the patient looks down, which results in the gas bubble moving backwards away from the tear. The three mirror contact lens is also tilted inferiorly so as not to lose contact with the cornea. When the contact lens is tilted down however, the most vertical (73°) mirror of the contact lens is now better suited for viewing an anterior tear.

We developed an alternative method which is illustrated in Figure 1. This requires the patient to look down, which results in the gas bubble moving backwards away from the tear (lower diagram). The three mirror contact lens is tilted inferiorly so as not to lose contact with the cornea, and the most vertical (73°) mirror is used. This contrasts with the more normal use of the contact lens when the eye looks straight ahead, and the intermediately tilted mirror (67°) of the three mirror contact lens is better suited for viewing anteriorly located tears (upper diagram). We successfully implemented this technique in both phakic and aphakic eyes following primary gas injection and following gas injection after a previous buckling operation. We recommend its use in such cases when the retinal tear is located in the superior 2 o'clock position of the eye.

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1 Tornambe PE. Pneumatic retinopexy. *Surv Ophthalmol* 1988; **32:** 270–81.
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BOOK REVIEWS

General Ophthalmology 1989. 12th Edn. Eds Daniel Vaughan, Taylor Asbury, Khalid F Tabbara. Pp 460. £26.65. Prentice-Hall: Hemel Hempstead, Hertfordshire, 1989.

The updated edition of the well known paperback came out in 1989. Because of its important position in the 'early postgraduate' part of the book market in British ophthalmology, it seems relevant to review it even at this stage. This 12th edition contains a number of changes including a specific chapter on lasers, a thoroughly revised chapter on neuro-ophthalmology (the editors have gone straight to the top, this chapter being written by Chavis and Hoyt), and a new section on low vision. Other parts have also been upgraded, including anatomy, embryology, and examination techniques. The strong chapter on ocular disorders associated with systemic disease (by Sanders and Graham) now includes a section on AIDS.

Chapters are laid out in a methodical fashion; basic sciences first, then examination and clinical material divided into broad groups. At the end there are appendices dealing with visual standards and aspects of visual function, a glossary of terms and a comprehensive index.

The main value of this book has always been to those who need more than an undergraduate textbook but have neither the resources nor desire to purchase one of the more substantial textbooks in this group which include Newell's *Principles and Concepts* and Kanski's *Clinical Ophthalmology*. This edition maintains this appeal, even enhancing it, at the same time containing considerable information and remaining brief.

Highlights include the chapter on examination (although the emphasis on Schiotz tonometry may puzzle young ophthalmologists in the UK) and the conjunctival chapter. The latter has always been a strong point and will continue to delight junior doctors who like learning lists. The general standard of the contributions is high with no major weak areas in content. Text is both easy to read and understand. A selection of references is given at the end of each chapter.

There are some minor flaws. The lack of colour plates must remain a problem to some potential buyers and the US bias of the appendices reduces their value on this side of the Atlantic. At this price it can be used intensively and discarded when the next edition appears.

Overall this will prove a useful book to junior ophthalmologists who need a ready reference when seeing unusual clinical presentations in the evening and at weekends, and to general practitioners taking an interest in ophthalmic diagnosis and treatment.

CHARLES SANDY
JOHN BRAZIER

World's Major Blinding Conditions. Edited by Arthur Lim Siew Ming. Pp 204. **Leaders in Ophthalmology in the Asia-Pacific.** Edited by Lim Kuang Hui. Pp 280. **Major Eye Centres of the World.** Eds Lim Kuang Hui, Arthur Lim Siew Ming. Pp 190. Complete set in case US$45.50 plus postage US$12. Published by XXVI International Congress of Ophthalmology, 1990, c/o Department of Ophthalmology, National University Hospital, Lower Kent Ridge Road, Singapore 0511.

This compendium of articles to mark the XXVI International Congress of Ophthalmology, Singapore, 1990, is presented as a trilogy. For the student of worldwide ophthalmology they provide a stimulating introduction to the huge variety of ophthalmological needs in the developing world – with descriptions of major blinding diseases, past and present achievements in the Asia-Pacific countries in prevention of blindness, and eye centres which contribute to the campaign against world blindness.

World's Major Blinding Conditions, published eight years ago as *Vision*, has been updated in this second edition. Well-known contributors in this field have discussed world blindness and its prevention, cataract, glaucoma, blinding malnutrition, blinding ocular infections, ocular trauma, and diabetic retinopathy. Trachoma and onchocerciasis deserve more space and emphasis within the text, and a section on leprosy and the eye would enhance the overall presentation. However, the text provides valuable information which will be a source of reference for those aware of these huge problems in eye care and will open the eyes of the uninitiated. The important issue of intraocular lens implant surgery versus traditional intracapsular cataract surgery in the developing world, including discussion of eye camps and alternative cataract surgical delivery services, is introduced.

Leaders in Ophthalmology in the Asia-Pacific. For readers interested in the origins of ophthalmology in many countries of the region and how our specialty has developed this volume gives fascinating background information. Besides single articles on individual countries the text broadens to include papers on the Asia-Pacific Academy of Ophthalmology, the World Health Organisation (Ophthalmic Training in the Third World), the International Agency for the Prevention of Blindness, and National Prevention of Blindness Campaigns and Eye Health Care. The title of the volume requires a delicate approach in presentation by the invited authors as each is a recognised leader in ophthalmology in his or her own country.

MURRAY McGAVIN

Major Eye Centres of the World is a short collection of self appraisals of contributing centres. This colourful tour of 24 ophthalmic institutions illustrates some of the variety of approach and thought that exists within our specialty. The largely common aims of the institutions are influenced by financial, cultural, personal, and government factors which emerge in the varying accounts.

IAN MURDOCH

Evoked Potential Manual: A Practical Guide to Clinical Applications. 2nd revised edn. Eds E J Colon, S L Visser. Pp 358. £86.00. Kluwer: London, 1990.

Evoked potentials are electrical changes elicited from the peripheral and central nervous system by a range of different stimuli. The subject extends into many different clinical specialties, and this multiauthor textbook provides a basic knowledge of the subject. There is a need to try and draw together such a diversity of techniques, but in a book of this kind it is not surprising that the clinical ophthalmologist will only find a short section relevant to the eye and visual pathway. Nevertheless the electrophysiologist will find the book to be a very useful and an excellent reference source.

N R GALLOWAY

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express), stating card number, expiry date, and full name.

OBITUARY

HANS GOLDMANN

Hans Goldmann was born in Komotau, Bohemia on 21 November 1899 and died 19 November 1991, shortly before his ninety-second birthday. He received a classical education at the Jesuit College in his native town, which now belongs to Czechoslovakia. He studied medicine in Prague and completed his doctoral thesis in 1923. In Prague he was assistant to A Tschermak-Seysenegg, the physiologist, and later to A Elschnig, one of the leading ophthalmologists and eye surgeons of his time. Those days with Tschermak provided the basis for Goldmann's future work and also for a long-lasting friendship with H Burian, who was his colleague. In 1924 he moved to Berne as assistant to A Siegrist, and in 1927 he became assistant medical director (Oberarzt). In 1930 he qualified as a university lecturer (Privatdozent), and in 1935 he succeeded A Siegrist as professor and head of the University Eye Hospital in Berne. From 1945 to 1946 he served as dean of the Medical School and in 1965 as rector magnificus of the University of Berne.

He spent sabbatical periods of varying duration at the Department of Ophthalmology, Washington University, St Louis, Missouri, at the time when B Becker led this thriving department. Many friendly relations were initiated at this time, such as those with Bob Moses, Jay Enoch, and many others. The exchange of young researchers between St Louis and Berne became an extremely fruitful habit.

After retiring in 1968 Goldmann still continued research until his eighties. Stereochronoscopy of the optic nerve head was his main contribution in this period. To visit and to talk with him was intellectually extremely rewarding, although he suffered in his last years from many illnesses. Certainly there is no other ophthalmologist, and probably no one else in any other field, who has left such an impression on his specialty like Hans Goldmann did, and this impression still has an effect in daily practice in the western world after almost 50 years: the construction of a new slit-lamp, the Haag-Streit 360 in 1933, later the Haag-Streit slit-lamp 900, which is still the world standard, then publication of the *Basics of exact perimetry* together with the introduction of the Goldmann perimeter in 1945, which set the standard for at least 40 years in perimetry until automated perimetry became used in daily practice.

His work on biomicroscopy of the chamber angle, of the central and peripheral fundus, and of the vitreous with the gonioscopic, the three-mirror Goldmann, and the 'macula' lenses in 1949, and the introduction of the applanation tonometer in 1956 provided the essential tools for the daily work of ophthalmologists around the world. He did not invent all these gadgets from scratch, but the ones already invented, like the slit-lamp, the gonioscopic lens, or the applanation tonometer, he changed into appropriately made, handy, easily applicable instruments.

Standing out among his many experiments, observations, and inventions are his work on cataract formation and on determination of the volume of production of the aqueous, his critical evaluation of tonography, his instrument for objective determination of visual acuity, the slit-lamp fluorophotometer, the instrumentation for cell count in the anterior chamber, and finally that for stereochronoscopy of the optic nerve head.

He was a keen observer and had a sixth sense for explication of clinical entities. As early as 1952 he implicated oxygen as being responsible for retinopathy of prematurity. He was certainly, for almost half a century, one of the world's experts in glaucoma. He was not only a scientist, but also a caring and beloved doctor of his patients.

His inventions and his scientific work fascinate by their modest expense and straightforwardness. His department did not emanate from quantity, but by the amount of thinking and brilliant discussions. Hans Goldmann's lectures to the students were the highlights of the curriculum of Berne. Being the inspiring teacher, he trained the majority of department heads and professors of ophthalmology in Switzerland, such as R Witmer, A Bangerter, P Niesel, F Fankhauser, G Eisner, G Schmitt, and also had some ophthalmic grandchildren, such as J Flammer, F Körner, and myself.

Hans Goldmann never gave a paper on the same subject twice. When, after a period of illness he could not present anything new, he refused to give the Fuchs Lecture in Vienna when he was about 70 years old. Later, he could still give the Aschoff Memorial Lecture. He received the Vogt Prize, was the first continental European to receive the Proctor medal, was awarded the Gullstrand, Gonin, Donders, and Graefe medals, and gave the Doyne, Montgomery, Arthur Bedell, and Proctor lectures.

Hans Goldmann's observations and experiments on thermal radiation and glass-blower's cataract, which led the young ophthalmologist to a 300-page-long academic battle with Alfred Vogt in *Graefe's Archives* in the 1930s, was in reality life-threatening for him, because he was a foreigner in Switzerland, and Jewish. If he had had to go back to Germany or to Czechoslovakia, his future would have become extremely doubtful, but what Swiss and world ophthalmology would have lost, if he had not received the chair in Berne, is unimaginable. Later, he became a Swiss citizen and, in his radiance, Swiss opthalmology could flourish.

He and his gracious wife, Erna, were perfect hosts in their homes in Brissago and Berne. There, she provided a peaceful yet stimulating refuge to which he could withdraw after his daily intensive activities in the Insel-Spital. His achievements are confirmation of her own great success in accomplishing that task.

To witness Goldmann's enormous knowledge in almost every field of science from archeology to history to physics – he read Newton in the original publications – and mathematics was extremely impressive. We have lost one of the giants of science, and we are proud that he worked for ophthalmology.

BALDER P GLOOR
ZURICH, SWITZERLAND

NOTES

European Society of Cataract and Refractive Surgery

The Xth Congress of the European Society of Cataract and Refractive Surgery will be held in Paris on 6–10 September 1992. Further details, Executive Office: Organisation 7, BP 77, 18 Avenue Egle, 78600 Maisons-Laffitte, France (Tel: 33 (1) 39 62 69 00. Fax: 33 (1) 39 62 28 08); or Scientific Office: Dr D Lebuisson, Congress, CMC Foch, BP 36, 92151 Suresnes Cedex, France. (Tel: 33 (1) 40 99 98 30. Fax: 33 (1) 40 99 98 49.)

Uveitis and retinal frontiers

The Francis I Proctor Foundation for Research in Ophthalmology of the University of California School of Medicine at San Francisco presents its 3rd Annual meeting entitled 'Uveitis and Retinal Frontiers' from 10–13 September 1992 at the Carmel Valley Ranch Resort, Carmel, California. Further details: University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742, USA. (Tel: (415) 476-4251.)

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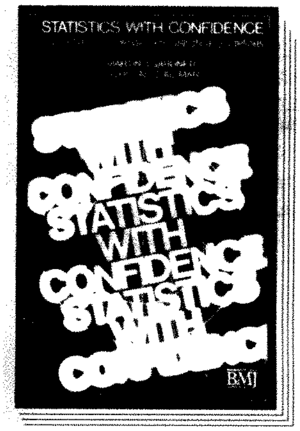

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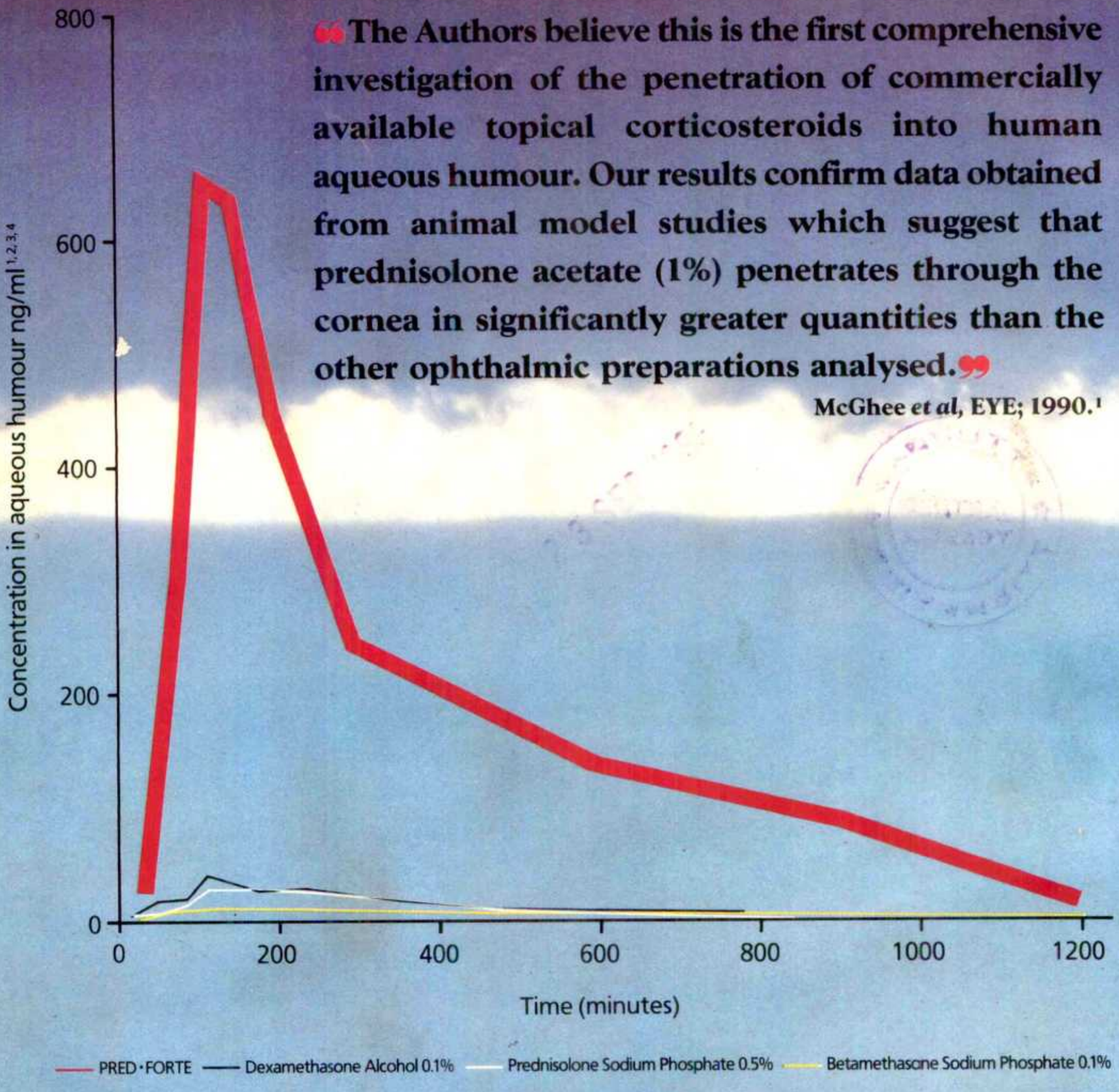
McGhee *et al*, EYE; 1990.[1]



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For routine inflammatory conditions of the eye

Pred Forte™ Abbreviated Prescribing Information

Presentation Sterile ophthalmic suspension containing prednisolone acetate USP 1.0% (w/v) preserved with benzalkonium chloride Ph Eur 0.006% (w/v) and disodium edetate Ph Eur 0.0127% (w/v). **Uses** For short-term treatment of steroid-responsive inflammatory conditions of the eye, after excluding the presence of viral, fungal and bacterial pathogens. **Dosage and administration** One to two drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to two drops every hour. **Contra-indications, warnings, etc** *Contra-indications:* Acute untreated purulent ocular infections. Viral diseases of the cornea and conjunctiva. Fungal diseases of the eye. Ocular tuberculosis. Hypersensitivity. *Warnings:* Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. Fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. Pred Forte contains benzalkonium chloride and should not be used in patients continuing to wear soft (hydrophilic) contact lenses. *Use in pregnancy:* Animal studies indicate there may be a very small risk of abnormalities of foetal development if corticosteroids are administered during pregnancy. *Precautions:* Patients with a history of herpes simplex keratitis should be treated with caution. Use of Pred Forte in the presence of stromal herpes simplex should be followed by frequent, mandatory, slit lamp microscopy. Use of topical corticosteroids may cause an increase in intraocular pressure in certain individuals. *Side-effects:* Ocular: Increased intraocular pressure; secondary ocular infections from fungi or viruses liberated from ocular tissues; perforation of the globe when used in conditions where there is a thinning of the cornea or sclera. Posterior subcapsular cataract formation has been reported. Systemic: Extensive topical use of corticosteroids may lead to systemic side effects. **Product Licence number** 0426/0051. **Basic NHS cost** 5 ml–£1.55; 10 ml–£3.09. **Product Licence holder:** Allergan Limited, High Wycombe, Bucks. HP12 3SH. Further information is available upon request to the above address. **References** 1. Penetration of Synthetic Corticosteroids into Human Aqueous Humour. McGhee C.N.J., Watson D.G., Midgley J., Noble M.J., Dutton G.N., Fern A.I., Eye 1990; **4**: 526-530. 2. Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humour. Watson D.J., Noble M.J., Dutton N., Midgley J., Healey T., Arch Ophthalmol 106, May 1988, 686-687. 3. Comparative Studies of the Penetration of Synthetic Corticosteroids into the Human Eye by GC-NICIMS. Midgley J.M., McGhee C.N.J., Watson D.G., Noble M.J., Healey T., Dutton G.N., J Pharm Pharmacol 1988 Dec; **4**(Suppl): 16P. 4. Penetration of Topically Applied Prednisolone Sodium Phosphate into Human Aqueous Humour. McGhee C.N.J., Noble M.J., Watson D.G., Dutton G.N., Fern A.I., Healey T.N., Midgeley J.N., Eye 1989, **3**, 463-467.

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